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THE LESIONS OF LEAD ENCEPHALITIS IN CHILDREN

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REVIEW

We are told that the clinical effects of lead poisoning on the brain were known to the ancients long before search for microscopical lesions was possible (1). The French writers, Grisolle and Tanquerel des Planches, are said to have given the first good clinical descriptions of lead encephalitis, written nearly a hundred years

ago (2, 3), and now it is familiar to all that young children with depraved appetite, or pica, may swallow plaster or chew paint from furniture, window sills, dolls and toys, and so develop symptoms of lead poisoning over a period of weeks or even months. Children, like lead workers, may develop abdominal pain, constipation and vomiting. Anaemia and basophilic stippling of red blood cells frequently develop, and sometimes a lead line appears on the gums. The urine contains not more than a good trace of protein usually, and in some instances glycosuria has been found (4). As the disease progresses the child becomes irritable and cantankerous, and finally stuporous. Visual disturbances, oedema of optic discs, elevation of blood pressure, and slow pulse may be observed. Projectile vomiting commonly occurs and convulsions generally appear for one or more days before death.

When convulsions set in, it is usually found that the pressure of the spinal fluid is increased; and the fluid contains increased quantities of protein, a few cells, and is sometimes xanthochromic (43). Lead may be demonstrated in the blood in abnormal quantity, and it was shown by Park (5) and by Vogt (6) that a curious disturbance in bone formation develops. The x-ray shows a dense shadow along the line of ossification where lead is deposited in the growing spicules of bone. The latter are found under the microscope to be more numerous than usual, and ossification is retarded. There are, too, characteristic intranuclear inclusion bodies in the kidney and liver (7).

As long ago as 1839 it was possible for Tanquerel des Planches to collect records of examinations of the brain in seventy-one instances of lead poisoning, although characteristic changes were not found to be common to all cases (8).[1] For a century the remarkably varied clinical manifestations of lead encephalitis have been recognized, and they are now perfectly familiar (2, 9). Nevertheless, examination of recent reviews on the subject and of modern textbooks of neurology and pathology shows that as yet no precise pathological lesions in the brain, responsible for the signs and symptoms, have been established as characteristic of lead poisoning (2, 10); and in a very recent monograph concerned with the clinical, anatomical and spectrographic study of the nervous system in acute metallic poisoning, Esser states that information is lacking concerning the changes caused by lead in the central nervous system of man (11).

The wide clinical interest aroused in recent years by the occurrence of acute lead encephalitis in children (12, 13, 14, 15, 16, 17, 18, 19), has been accompanied by few corresponding anatomical studies. The opportunity has lately been afforded to make systematic microscopical examination of the brain in a large series of cases which show an astonishing variety and number of lesions. Similar changes have not been described in any other disease of the central nervous system, and since they appear to be characteristic of lead poisoning, it seems

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[1] No lesions were seen in some cases. Yellow discoloration was found in some, and in still others the brain was enlarged or atrophied.

worthwhile once more to review some of the literature devoted to the subject and to describe the characteristic lesions at some length.

In 1888 Westphal reviewed the cases which had been reported (3), and stated that Kussmaul and Maier in 1872 were the first to make histological examination of the brain in lead encephalitis. They examined one case and found wide homogeneous areas around blood vessels in the gray matter, interpreted as increased perivascular connective tissue (20). Von Monakow reported a case in 1879 which showed gross atrophy of the brain, and widening of the adventitial space about blood vessels, together with multiplication of nuclei, collections of cells, fat droplets and pigment. He also described hyperplasia of neuroglia, many minute haemorrhages in the white matter, and numerous abnormal ganglion cells (21). In Seifert's case, reported in 1884, the brain was atrophied and the basilar artery was sclerotic. There was abundant fluid in the subarachnoid spaces and two small gross haemorrhages were found in the brain (22). Likewise Oppenheim, describing one case in 1885, found gross cerebral haemorrhages in a patient with hemiplegia (23). Westphal could find only a small haemorrhage in the left uncinate gyrus of one case and in another several areas of softening together with sclerosis of blood vessels. He assumed that lead caused fine histological changes which could not be detected by the methods then available, though he himself made no microscopical examinations (3).

Following Westphal in 1900 Courtney reported another case with gross cerebral haemorrhages occurring in an adult (24), and in 1912 Cadwalader found a large cerebral haemorrhage in his case, without mention of the cerebral arteries. He described thickening of meninges, increased neuroglia in the cortex and chromatolysis of the Betz cells (25).

Three cases were studied microscopically and reported in 1921 by Hassin (26). Slight changes in nerve cells were found, such as fat accumulation and chromatolysis, and proliferation of endothelial cells, adventitial cells, and of new blood capillaries. Glial cells in excess along blood vessels in the cerebral cortex and cerebellum were found, and thickening of the meninges. There was some infiltration of the meninges with lymphoid cells, and granules of green pigment were found in the brain.

The whole subject of lead poisoning was reviewed at length in 1925 by Aub, Fairhall, Minot and Reznikoff who pointed out the discrepancy between the well-known clinical manifestations and the meagre anatomical findings which had so far been described in the literature (2). Changes in the spinal fluid, the presence of cells, high pressure and increased quantities of protein, were reported in several papers between 1905 and 1924; and on this basis, without examination of the brain, Suzuki and Kaneko speak of serous meningitis in children, caused by lead poisoning acquired from white powders used by Japanese mothers as a cosmetic for the skin (17). From consideration of the changes in the spinal fluid and the histological lesions reported by Hassin it was suggested in the review of Aub, Fairhall, Minot and Reznikoff, that "in so-called lead encephalopathy the meninges are primarily involved, or in other words that the disease is really a meningo-

pathy". They concluded that further information concerning the action of lead on the tissues was not possible from postmortem studies, since its action was apparently too subtle to yield to this type of investigation.

Between the years 1928 and 1934, however, several papers appeared describing new lesions which were found by independent observers. Freifeld reported two cases, lead workers, one in 1928 and one in 1933, showing focal destruction of nerve cells replaced by neuroglia in the cerebral cortex, basal ganglia and pons. She found extraordinary destruction of Purkinje cells in the cerebellum, associated in some areas with new growth of glia. Lesions in the dentate nuclei and thrombi in small vessels were described, in some instances leading to necrosis of tissue. Small perivascular calcium deposits and granules of brown pigment in phagocytic cells were found, and there were perivascular haemorrhages in all parts of the brain. She expressed the opinion that all of the lesions were dependent on vascular damage (27, 28).

In 1929 Tuthill also described focal scars of neuroglia (glial rosettes) in the cortex, basal ganglia, and cerebellum of an infant, and she too saw extensive destruction of Purkinje cells in the cerebellum and gliosis of the molecular layer (29). Scattered minute haemorrhages were found and Tuthill described for the first time lesions which were called concretions. These were scattered in many parts of the brain and cerebellum, and in the walls of blood vessels. They varied in size from small globules to large masses 100 micra in diameter, stained with basic dyes and contained iron. They were thought to be "albuminoid break-down products." It is significant that the patient, a child of 2½ years, after an initial attack of encephalitis, was free from symptoms for about two months before manifestations reappeared and death occurred.

Staemler reported a case in 1929 which he says was essentially like the first case of Freifeld (30), and in 1933 McKhann and Vogt, from consideration of the clinical signs and symptoms, suggested that they might depend on increased intracranial pressure due to intense cerebral oedema (9).

Four more cases, occurring in lead workers, were described in 1933 by Winkelman and Eckel who found lesions in the capillaries, numerous focal lesions in the gray matter of the cerebral cortex, and mentioned the presence of granular perivascular material as evidence of cerebral oedema (31).

The next year, in 1934, Rhea reported a single case in which he saw multiplication of cells in the walls of capillaries and free fluid microscopically in the meninges (32). The conspicuous appearance of the blood vessel in the brain, interpreted by some authors in the past as newly formed growing vessels (26) appeared to Rhea to depend merely on dilatation, and there were a few disseminated microscopical haemorrhages.

THE CLINICAL CHARACTERISTICS IN TWENTY-TWO CASES

Twenty-two cases are described here, all occurring in children. The evidence of lead poisoning is clear in each instance and is shown

in Table I. Most of the cases occurred in colored infants between 13 months and $3\frac{1}{2}$ years of age. One was in a boy of seven, however, and one in a girl of 6 years. Five were white children.

In most cases lead was ingested by nibbling painted articles, usually furniture. Paint may be swallowed in this manner for many months (5 to 18 months in this series) before the onset of neurological disturbances. In one case lead fumes were inhaled from old automobile battery casings burned in the cook-stove. For a period of 3 years after the original convulsions the blood lead remained elevated, and the x-ray showed lead lines in the bones. The child finally died in convulsions and the brain showed both old and fresh lesions, although no evidence could be obtained of exposure to lead fumes or ingestion of lead in the interval. In a second case the first convulsion occurred a month before death, and in a third the child lived for about 6 weeks after the onset of peripheral neuritis. The neurological signs and symptoms were of short duration in the remainder of the cases.

It is curious that 19 of the 22 cases occurred during the five months including June and October, and the tendency of lead encephalitis to appear during the summer and early fall has been mentioned before by Suzuki and Kaneko (17), and by Fukushima and Matsumoto (18), although no explanation was evident.

Complete records of the temperature from the onset of convulsions are not available, but in 21 of the 22 cases fever was present during the stay in the hospital. The temperature was usually irregular and in most cases several degrees of fever were present at times. It would seem from the microscopical sections that the lesions in the brain are sufficient to account for elevation of temperature. There is the possibility, however, discussed in another section of this paper, that fever or the elevated atmospheric temperature of summer and fall may supply the factors which initiate the vascular changes in the brain which in turn are followed by exudate of serous fluid into the tissue.

A marked leucocytosis was observed in most of the cases. The count was 30,000 or above in four of the cases, above 20,000 in eight others, between 10 and 19,000 in seven cases, and normal in two cases. In one case no white count was made, and in a case in the first group there were 58,500 white cells per cu.mm. The degree of leucocytosis

TABLE I

Evidence of Lead Poisoning

AUTOPSY NUMBER	HISTORY OF LEAD INGESTION	LEAD LINE ON GUMS	ANAEMIA	STIPPLED RBC	ELEVATED BLOOD LEAD	LEAD LINE IN BONES		NUCLEAR INCLUSIONS
						X-ray	Microscopic	Kidney and liver
5940	Pica	+	+	+	No exam.	No exam.	+	+
7532	+	0	+	+	No exam.	No exam.	+	+
10465	+	+	+	+	No exam.	No exam.	+	+
10637	+	0	+	+	No exam.	No exam.	+	+
10850	+	0	+	+	No exam.	No exam.	+	+
11766	+	No exam.	No exam.	No exam.	No exam.	No exam.	+	+
12168	House paint on hands	0	+	+	No exam.	No exam.	+	+
13334	0	+	+	+	Elevated	+	+	+
13698	+	+	+	0	Elevated	+	+	+
13726	0	0	+	+	Elevated	+	+	+
13795	+	0	Slight	0	Elevated	+	+	+
13830	+	0	+	+	Elevated	+	+	+
14057	+	+	+	+	Elevated	+	+	+
14287	Pica	0	+	+	Elevated	+	+	+
14307	+	0	+	0	Elevated	+	+	+
14336	+	+	+	0	Elevated	+	+	+
14352	+	0	0	+	Elevated	+	+	+
14354	Exposed to lead fumes	+	+	0	Elevated	+	+	Few
14370	Pica	+	+	+	Elevated	+	+	+
14849	+	0	+	+	No exam.	+	+	+
14954	+	0	+	+	Elevated	+	+	+
14974	Pica	0	+	+	?	+	+	+

seems out of proportion to the anaemia in many cases, and is not apparently to be correlated with infection. At least no evident infection was discovered at autopsy in many of the cases.

The anaemia which was present in the majority of cases was not very marked, and a reduction of the haemoglobin to 50% or less was found in only eight cases. In sixteen cases basophilic stippling of red blood cells was seen in the smears, and nucleated red cells were recorded in six of the clinical histories.

Characteristic changes were seen in the bones by x-ray in all cases that were examined (15 cases), and were found in microscopical sections in every case. Eosinophilic nuclear inclusion bodies, also typical of lead poisoning, were present in liver and kidneys of all of the cases.

The familiar changes in the spinal fluid—increased pressure, increased protein, and moderate numbers of cells—were found in the present group of cases. The cells in the spinal fluid are usually said to consist chiefly of lymphocytes (42), (13), (2), in lead encephalitis. In this series, as pointed out again later, the majority of the cells in the meninges are "mononuclear" cells, but they originate from the substance of the brain and are forced out into the meshes of the meninges by exudate which distends the molecular layers of the cerebral cortex and cerebellum.

A variety of clinical manifestations appeared in many cases long before the onset of definite neurological signs and symptoms. Malaise, anorexia, loss of weight, abdominal pain, headache and constipation are all familiar. Changes in behavior were noticed in many children. Some were nervous, irritable, fretful and restless. One child was noisy and disobedient, developed enuresis and a tendency to bite and scratch. Long crying spells and screaming fits were described and a tendency to be easily frightened. One child was nervous and cranky.

Vomiting was a common complaint, and was present in twenty of the cases. It was described as projectile in a few cases. In two of the cases vomiting first appeared one to two days before death; in eight cases one to three weeks before convulsion. More often there was a history of vomiting at times for a month or more before the onset of more definite manifestations of encephalitis.

Towards the end drowsiness, stupor and a deep coma appear, usually in association with convulsions. One child fell unconscious on the

street for several minutes, regained consciousness, and later on the same day had convulsions.

Generalized clonic convulsions developed in nearly all cases, but one child showed nothing more than alternate periods of spasticity and flaccidity. In some cases, after attacks of vomiting, the children were described as becoming limp and then comatose.

In most instances the convulsions became generalized and were frequently repeated. At first, however, they were unilateral in some cases, or one side and then the other was affected before the convulsions became generalized. Strabismus and nystagmus were frequently observed in association with convulsions.

The pulse was slow in some cases, rapid and irregular in others. The blood pressure was not studied in general, but was found elevated in a few cases. Respirations were often slow, sometimes irregular, and were described as gasping in some cases.

In two cases there was clinical evidence of peripheral neuritis in addition to encephalitis. The peripheral nerves were not examined at autopsy in one of these, but the other showed widespread peripheral lesions, as described elsewhere (33).

THE ANATOMICAL MATERIAL EXAMINED

In ten of the cases relatively few sections of the brain and spinal cord have been available for microscopical examination, since at autopsy few (from 2 to 11) blocks of tissue were cut. This number in two instances includes a section of each retina.

Many blocks were prepared, however, from all lobes of the cerebral hemispheres of the twelve cases autopsied in recent years. The number of blocks varied from 30 to 65 in the different cases. In each instance blocks of the cerebellum varying in number from 4 to 11 were cut at autopsy and the corresponding microscopical sections were examined. The basal ganglia, mesencephalon, pons and medulla of the recent cases were examined and sections were made from a number of blocks (table II). One or two blocks were taken from the cervical part of the spinal cord in most cases and in three cases sections from the cervical, thoracic and lumbar portions of the cord were examined microscopically.

In most instances the body was embalmed with the brain *in situ*, the fluid containing about 3 per cent of formalin. After removal the brains were hardened in 10 per cent formalin and blocks were then cut, dehydrated, and embedded in paraffin. In a few cases additional blocks were fixed in Zenker-formol at autopsy after the body was embalmed.

In order to determine whether or not the fluid exudate found microscopically in the brain and the distortion of the normal architecture were influenced by the

embalming and dehydrating processes, the brain was removed before the embalming was begun in three cases (Nos. 17, 18 & 21), and blocks were cut immediately and fixed in 10 per cent formalin; and the blocks from one unembalmed case (No. 18) and from two of the embalmed cases (Nos. 20 & 22) were dehydrated very slowly, beginning with 30% alcohol and increasing the strength of alcohol 10% with each period of dehydration. In these control cases coagulated exudate and abnormal distortion of architecture are found as in the others. The disturbances in the architecture are the result of exudate which escapes into the tissues from damaged blood vessels and is partly dissolved in the fixing fluid. The lesions are described below in detail.

The posterior half of each eye was removed and fixed in Bouin's fluid in five of the cases, and microscopical sections were made showing the retina and optic disc. Blocks of the hypophysis were fixed in Zenker-formol at autopsy in seventeen cases, and the pineal body, usually fixed in formalin, was examined microscopically in eight cases.

THE GROSS APPEARANCE OF THE BRAIN

It has long been recognized that in acute lead encephalitis associated with convulsions, the brain at autopsy may appear large and soft with broad, flat convolutions, and narrow, obliterated sulci. In some of the cases of Tanquerel des Planches the convolutions were flattened, and the depressions between them had disappeared (8). Traube, in 1870, said that Tanquerel des Planches found the brain to be anaemic and swollen (34), and it is said by McKhann that Chvostek in 1897 described a case with swollen brain, flattened convolutions and medulla pressed into the spinal canal (19). The swollen appearance of the brain has become familiar and, without any clear microscopical descriptions of the tissue, it has been inferred from the external appearance that the brain is oedematous (35, 36). McKhann and Vogt (9) especially have pointed out that the clinical signs of encephalitis may depend on accumulations of fluid in the brain.

In this series of 22 cases it was often but not always recognized at autopsy that the brain was larger and softer than normal. Unusually broad, flattened convolutions, and narrow sulci, more or less obliterated, were described in the protocols in many of the cases. In many instances a well marked pressure cone was recognized at the base of of the cerebellum, like that described by Blackfan (44) in association with acute nephritis in children.

These external changes have been observed in all of the twelve cases

autopsied in the past two years, and in addition certain other manifestations of the presence of fluid in the substance of the brain. The gray matter has been found to be thicker and more translucent than normal and the freshly cut surface of the brain very wet.

The gross specimen may be pale and has frequently been so described in the literature. The external surface may be hyperaemic and inflamed in appearance, however, and this has been observed in a number of the cases. On section, too, minute dilated blood vessels in the white matter have been conspicuous in some cases, and may be difficult to distinguish from punctate haemorrhages. In one case such haemorrhages were very numerous and distinct in the gross specimen, and they were readily recognized because microscopically each haemorrhage forms a ring about a central area of necrotic tissue which is usually associated with a capillary thrombus.

ON THE PRESENCE OF PLASMA PROTEIN IN EXUDATE WHICH ESCAPES FROM THE BRAIN INTO THE FIXING FLUID

The gross appearance of the brain indicates that it is distended with fluid, and microscopical sections show a part of the fluid coagulated about the blood vessels and far out in the tissue. The exudate is identical in appearance with serum in the blood vessels, and both the serum and fresh exudate are evidently coagulated by the fixing fluid.

A portion of the exudate, however, escapes into the fixing and dehydrating fluids. If several blocks of the unembalmed or freshly embalmed brain are dropped into a small jar of alcohol, the latter, by virtue of its dehydrating action, rapidly withdraws the serous fluid and a milky precipitate forms at once, thus indicating the protein content of the exudate.[2]

Microscopical sections of material thus fixed in alcohol show less of the exudate coagulated in the tissue than is seen in sections of material fixed in formalin. But the latter has an abnormal vacuolated and distorted architecture in many places, indicating that the thinner watery portion of the exudate, poor in coagulable protein, is either slowly dissolved by the formalin or extracted later by the dehydrating fluids.

[2] Blocks of the normal brain produce a faint cloudiness in alcohol.

Staining methods useful for the detection of coagulated serous exudate in the brain are described in Appendix I (p. 37).

THE MICROSCOPICAL LESIONS IN THE CEREBRAL HEMISPHERES IN ACUTE CASES

On microscopical examination very numerous lesions and a variety of changes are found which affect the blood vessels, the gray matter, and the central white matter of many convolutions. Dilated and narrowed capillaries, necrotic vessels and capillary thrombi, minute haemorrhages, fresh and old serous exudate permeating, stretching and tearing the tissues, small foci of necrosis, fat-laden cells, necrotic cells and other lesions are all present; and the same variety of lesions is found in each case. It is to be emphasized, however, that each type of lesion is not usually seen in every microscopical section, and in some sections few changes may be recognized. All of the lesions are indeed somewhat patchy and irregular in distribution in every case, but examination of many sections shows that actually there are widespread lesions of like appearance in many parts of the brain. The intensity of the damage, the number of microscopical lesions, and the quantity of visible exudate are not the same, however, in every case.

In order to see the thinner films of perivascular exudate, and to fully appreciate the changes in nerve cells and in the nuclei of cells in the walls of capillaries, it is necessary to examine the sections carefully, and under the oil-immersion lens.

The Blood Vessels. Most of the lesions in the brain seem to be directly dependent on damage to the arterioles and capillaries. The changes in the vessels are like those caused by many other injurious agents, and they are quite like the vascular alterations ordinarily found at the site of any acute and subacute inflammation. Vessels in the meninges and in the gray and white matter are affected, and in the white matter all of the lesions are especially pronounced in the apical portion of the central white tissue of each convolution. Lesions in the vessels and exudate in the tissue are much less abundant far out towards and directly in the more densely packed fibres of the centrum semiovale, in the compact internal capsule, and in the corpus callosum.

Many capillaries are filled with red blood cells and look dilated;

and not infrequently, on examining many sections, dilated capillaries stuffed with polymorphonuclear leucocytes are found. Such dilated vessels may be surrounded by thin irregular films or wider rings of serous exudate in which rarely one or two polymorphonuclear leucocytes are found. In some cases, perhaps the most acute, the dilatation of the capillaries is very conspicuous.

In other cases some capillaries are dilated, but many more have narrow lumina which may contain no red blood cells for a long distance and are filled with serum. These narrow capillaries are probably contracted, and some of the nuclei in the walls of many of them are swollen, while some are necrotic, pyknotic and broken into several fragments. About many of them there are films, rings, or droplets of exudate.

In most of the cases a few necrotic capillary loops occluded by thrombi are found in gray and white matter, and in some occluded necrotic little vessels are very numerous. The nuclei in the walls of the occluded loops are pyknotic and fragmented. Usually fresh or older films of exudate and droplets of exudate are found in clusters about the occluded capillary loops.

The nuclei of cells in the adventitia of many arterioles, and in the walls of the dilated and narrowed capillaries which are not necrotic are in general swollen and vesicular in appearance. There is evidence of multiplication of these nuclei, and one can readily find groups of three or four at a point where one nucleus should normally be found. Rarely, too, a mitotic figure may be seen in such a nucleus.

Most of the swollen nuclei and the new clumps of nuclei project outward from the walls of the capillaries, not into the lumina. This may be observed especially in segments of small vessels which are closed, with opposite walls in contact. We have found no evidence of sprouting or actual new formation of capillaries, however, as described by Hassin (26), and Winkelman and Eckel (31). The vascular appearance of the tissue which is seen in some cases can be accounted for by dilatation of the capillaries, as already suggested by Rhea (32).

Aside from dilatation and narrowing of the capillaries, and the swelling, multiplication and necrosis of nuclei, it may be pointed out that the thinner films of exudate about the vessels may give the appearance of thickened capillary walls. The irregular outer margins of the fluid,

the variable thickness about a given capillary, and the identity of its appearance with the exudate which forms wider pools about vessels, all go to show that the thin films are composed of coagulated exudate. The walls of the capillaries seem to be permeated by the fluid, however, as well as surrounded by it and may therefore appear to be continuous with the exudate.

Occasional small arteries are found in some of the cases with areas of hyaline necrosis of the media and pyknosis and fragmentation of the nuclei of the muscularis. Such arterioles may contain thrombi, and exudate and new glial cells are found in the spongy tissue about them.

Fresh Serous Exudate Coagulated by the Fixing Fluid. Most of the exudate consists of fluid which has the appearance of serum and stains precisely like serum in the blood vessels. From this it may be inferred that during life this portion of the exudate, like the blood, was in a fluid condition, and that both the serum in the vessels and the serous exudate outside are coagulated by the formalin used to fix the blocks of tissue. The exudate generally contains no fibrin (phosphotungstic acid-haematoxylin), and only occasional polymorphonuclear leucocytes are found in it. The freshly coagulated exudate is found about blood vessels in all of the cases, and in fifteen cases there are large areas in the gray or white matter diffusely permeated by serous fluid.

The perivascular fluid forms narrow rings and wide pools which surround capillaries and arterioles and vary in width. The fluid about numerous capillaries forms exceedingly thin films with irregular wavy margins, or, when more abundant, it may extend outward for a distance of 2 or more micra. The collections of exudate are wider around arterioles, and are especially conspicuous in the central and apical white matter where the fibres are relatively few in number and the tissue is less compact and more readily pushed aside by fluid than in the denser grey matter. The rings of homogeneous exudate about vessels in the white matter may extend outward for a distance of 150 or 200 micra. Diffuse exudate appears under the high power of the microscope as fine granular material between and adherent to the fibers. In the meninges the exudate may be very abundant, and often extends far out from the vessels on the surface, while the sulci may be more or less completely filled.

Irregular microscopical foci of variable size, whole microscopical fields, and confluent patches occupying most of the grey matter of a given convolution, may be diffusely infiltrated by the protein-filled exudate. Such areas stain very deeply and irregularly with eosin and may be recognized under the microscope and also by the naked eye. Microscopically they are homogeneous and hyaline in appearance, and the normal striation dependent on the parallel arrangement of the cells and fibres is distorted. The use of safranin and light green brings out the red color of the diffuse exudate in a surprising way, and in contrast to the neighboring grey matter which is not infiltrated and consequently stains green. (See Appendix I for Staining Methods.)

Inspissated Exudate Coagulated in the Tissues about the Capillaries. Besides the fresh serous exudate there is, in addition, a perivascular material in the form of small drops which differ somewhat in appearance from the serum coagulated by the formalin, and are especially numerous about narrowed capillaries in the gray matter. Their perivascular location and association with damaged capillaries, and their staining properties, indicate that they represent somewhat older inspissated exudate, coagulated in the brain before the blocks of tissue were fixed by the formalin.

Rows and clusters of these small round drops of exudate are found in the gray matter on one side and along the margins of many capillaries in most of the cases, and some are also found about vessels in the white matter. A single drop may completely surround a capillary segment, and the origin of some of the droplets from the fresh serous fluid may be observed. Occasionally there are small drops incompletely separated from the margin of a film or wider ring of fresh perivascular serous exudate. These little drops, caught in the process of forming, have round margins but remain attached at one point to the main mass of perivascular serum; and they stain almost exactly like the serous fluid fixed by the formalin.

Most of the droplets, however, are somewhat more deeply stained with eosin than the fresh exudate, and they are a little more homogeneous, hyaline, and refractive. They are variable in size and number. Numerous minute drops, less than 1 micron in diameter, may be found closely applied to the wall of a capillary. More often the droplets along one margin of a capillary form clusters, 50 to 60 micra in diameter,

in which the individual drops may vary from 1 to 20 micra or more in size. Some clusters of irregular outline measure 80 or more micra in largest diameter, and in general there is great variation in the size of the clusters and individual drops of exudate. Many droplets are 4 to 12 micra in diameter. Larger ones, 20 to 30 micra in size, are quite numerous, and some measure 50 micra in diameter.

Droplets of exudate are found especially about the damaged capillaries which look narrowed and show swollen or pyknotic and fragmented nuclei. They are also found about necrotic capillary segments filled with hyaline thrombi. The fresher films and rings of exudate are found more especially around dilated capillaries.

In one of the cases (No. 17) there are a few large masses of granular exudate 70 micra in largest diameter, which contain pyknotic nuclear fragments and a few polymorphonuclear leucocytes. These masses resemble old fibrinous exudate but contain no fresh threads of fibrin. Serofibrinous exudate was found in only one of the cases (No. 4) in which intense capillary damage was evident and necrotic capillary segments were very numerous.

Old Exudate and Old Vascular Lesions which Contain Iron and Basophilic Material Resembling Calcium. It is evident that the round drops of perivascular exudate originate from the serous fluid which escapes from the damaged blood vessels. The apparent increased density of the drops, and their somewhat inspissated appearance, suggest that they were hardened or coagulated in the tissue before death. Further proof of their antemortem coagulation is offered by the changed appearance of the perivascular droplets in cases of long duration.

In this series of cases the clinical evidence of marked cerebral damage (coma and convulsions) usually appeared several days or a few hours before death occurred, and in these the droplets of exudate appear to be somewhat older than the very fresh rings of serous exudate. In one of the cases, however (No. 5), the first convulsion had appeared a month before the child died. Most of the perivascular droplets in the brain are slightly basophilic, staining purplish-red with haematoxylin and eosin. In other respects they resemble the eosinophilic droplets of exudate found in the cases of short duration. In two cases of still longer duration (No. 7 and No. 18) there are very

numerous deeply basophilic drops about many small blood vessels. In haematoxylin stains they look precisely like calcium salts and contain iron (Prussian blue reaction). With increasing basophilia they show a series of concentric circular strata. In their perivascular location, their predominance about vessels in the gray matter and in their variation in size, they are quite like the eosinophilic droplets which occur in the cases of short duration. From this it seems clear that the collection of stainable iron in the drops and their basophilic calcium-like appearance represent changes which have gradually developed over a considerable period of time. Such changes do not occur in perfectly fluid serous exudate, and it seems evident that by means of an unknown mechanism the perivascular eosinophilic droplets are coagulated in the brain where they may remain for months or years, gradually accumulating iron and basophilic material which stains like calcium salts. The clotting of fibrin is not concerned in the process, for no fibrin can be demonstrated in the freshest serous fluid in the majority of the cases.

Besides the basophilic drops of old exudate there are basophilic areas in the intima and media of arterioles in three cases (Nos. 7, 17 and 18). Similar lesions were seen in the case reported by Tuthill (29), and they are precisely like foci of necrosis and calcification commonly seen in association with arteriosclerosis. Such delayed changes developing slowly after the initial injury serve to emphasize the harmful effects of lead on the cerebral blood vessels; but proof is lacking that the basophilic precipitate in the vessels and exudate is actually calcium since it is not readily dissolved by weak acids and since crystals of gypsum (calcium sulphate) do not appear when the sections are treated with sulphuric acid. Furthermore, as in the case reported by Tuthill, it has been found impossible in the present series of cases to demonstrate the presence of lead in the basophilic exudate by means of the histo-chemical methods now available.

The Effect of Exudate Coagulated in the Tissue and of Exudate Lost in the Fixative on the Architecture of the Brain. Microscopical sections of the normal brain fixed in formalin and stained with haematoxylin and eosin show the nerve cells of the cerebral cortex arranged in regular vertical columns parallel to each other. Likewise it is evident under the high power of the microscope that the majority of the fibres

in the gray and white matter, while not specifically stained by eosin, are arranged in vertical parallel rows. The architecture is therefore characterized by a delicate striation determined by the direction of the majority of the cells and fibres. The striation in the gray matter is very delicate and the parallel lines are compact and very close together. In the central white matter of each convolution, on the other hand, the striation is coarser and less compact in appearance and the actual fibrous nature of the striae can be seen in sections stained with haematoxylin and eosin.

The outpouring of exudate into the brain produces a marked disturbance of the normal architecture. The fibres are separated, stretched and torn by the infiltrating fluid, and the orderly arrangement of cells and fibres in parallel columns is lost. Where the exudate is coagulated and stained, the tissue looks smooth and homogeneous instead of striated. In areas from which the fluid has disappeared the normal striated tissue has been converted into a tissue of spongy texture in which the cells are irregularly scattered.

In most of the cases the gray and white matter of many individual convolutions exhibit such a porous architecture in a diffuse or patchy way except in the areas which are filled with coagulated exudate. There are, in addition, certain zones where the change is especially marked and the porous texture is especially coarse. These areas are found about arterioles in the white matter, in circumscribed foci about capillaries scattered irregularly in the gray and white matter, in a long narrow zone at the junction of gray and white matter, in the superficial part of the molecular layer of the gray matter, and in large portions of the whole central white matter of single convolutions from which the exudate has more or less disappeared.

The perivascular accumulations of serous fluid and of older droplets of exudate coagulated about the capillaries push the cells and fibres away from the walls of the vessels. The width of the gaps produced and the distortion of the architecture depend on the quantity of exudate. Perivascular pools of fluid about arterioles are especially wide in the white matter, and usually a little neuroglia, together with frayed, torn adventitial fibres, is left near the walls of the arterioles and scattered in the fluid exudate. Outside these periarteriolar rings of fluid the white matter in a circular zone of varying diameter is often ex-

tremely porous. Many fibres have disappeared, leaving the remainder widely separated from each other. Similarly, in some cases much of the whole central white matter or its apical portion in some convolutions may be diffusely altered in the same way. In both perivascular and diffuse areas many of the remaining axis cylinders are poorly stained and broken into numerous irregular fragments (Bodian's silver stain for axis cylinders). Indeed the tissue that remains is necrotic and disintegrating and the glial nuclei are pyknotic.

In many of the cases there are conspicuous sharply circumscribed clusters of holes in the gray and white matter. They are usually found grouped around or at the margin of a capillary, and vary from 20 to 600 micra in longest diameter. The individual vacuoles in a given group vary from 2 to 50 micra in diameter. In many of the clusters some of the vacuoles contain coagulated serous exudate, while most of them are empty. The tissue at the margins of the clusters and between the holes in each group is compressed and stretched, and some fibres are obviously torn.

A similar irregular porous change of finer texture is often found diffusely in a long zone 200 to 400 micra wide at the junction of the gray and white matter of many convolutions. Here, too, some of the spaces may contain coagulated serous exudate, while the majority are empty. The fibres between the spaces are compressed, stretched, and torn.

In all of the acute cases there are numerous superficial patches in the molecular layer of the cortex where the tissue is very coarsely vacuolated. These patches vary in size and are found on the surface and deep in the sulci. Here again some of the spaces contain coagulated exudate which escapes from capillary vessels penetrating the brain from the meninges. The collection of fluid in these superficial patches lifts up and tears the inner layer of the pia mater from the brain, and propels glial cells into the subarachnoid space. In many places the pia may be elevated from 25 to 50 micra above its original level.

The Neuroglia. In association with the lesions produced in the fibres of the white matter by the presence of exudate, certain characteristic changes in the cells are also usually found. New cells, damaged cells with fat-laden cytoplasm and necrotic cells may all be recognized.

In the spongy patches of the molecular layer there are numerous small groups of abnormal glial cells. The arrangement of the cells in groups and the presence of occasional mitotic figures indicate that there is proliferation of neuroglia. Most of the cells resemble fibrous astrocytes. They are large, and may measure 12 micra in diameter. The cytoplasm of many is homogeneous and hyaline, and the nuclei are large and vesicular. In sections stained with haematoxylin and eosin processes are readily seen emerging from the angular margins of the cells, and specific stains (phosphotungstic acid-haematoxylin) show the processes to be neuroglia fibres. The cytoplasm of some of the cells is foamy and vacuolated in appearance due to the presence of fat droplets (Scharlach R; osmic acid), and occasional cells contain fine yellowish-brown granules of pigment. Some cells are rounded and apparently are no longer connected with neuroglia fibrils. Some of these have foamy fat-laden cytoplasm and many of them are necrotic, with pyknotic nuclei. Such necrotic cells may be found lying free in the meshes of the meninges, evidently dislodged and forced outwards by the fluid which stretches and tears the fibres of the molecular layer and lifts up the pia mater.

These damaged and necrotic glial cells make up the great majority of the cells found in the meninges in all of the cases. In the cases in which the cells found clinically in the spinal fluid were most numerous, 25 to 66 per cu.mm., the microscopical sections show a good many of the altered glial cells in the meshes of the pia mater, and practically no leucocytes of any kind. This suggests that most of the so-called lymphoid cells in the spinal fluid in lead poisoning are not leucocytes from the blood; and certainly many of them are cells dislodged from the surface of the molecular layer.

Somewhat similar changes are found in the glial cells of the central white matter of many convolutions. The abnormal cells are especially conspicuous in the apical part of the central white matter and in the narrow spongy zone at the junction of the gray and white matter. Scattered more or less diffusely in these zones there are: (1) large astrocytes with vesicular nuclei, hyaline cytoplasm, angular bodies, and evident neuroglia fibrils; (2) occasional cells in mitosis; (3) some foamy fat-laden cells; and (4) round necrotic cells with pyknotic nuclei. In the cases in which the white matter is diffusely saturated with very abundant coagulated serous fluid, many of the glial cells are necrotic,

and few of the new swollen astrocytes are found (Cases 6, 15, and 19). In other cases where the central white matter is particularly spongy and distorted by fluid which was evidently poor in protein and dissolved in the fixing agent, many of the large swollen astrocytes are found and relatively few necrotic cells (Cases 11, 21 and 23).

In most of the cases foamy fat-laden cells and a few cells which contain granules of yellowish-brown pigment are found about arterioles in the white matter. Very few are to be seen in some cases, while in others the cells may be present in moderate numbers about many little arteries. They are apparently damaged glial cells and are identical in appearance with the foamy and pigmented cells in the spongy patches of the molecular layer. The origin of the foamy fat-laden cells from damaged neuroglia can be seen in many places where the fluid which collects in rings and pools about arterioles tears a gap in the perivascular tissue, leaving a narrow ring of neuroglia attached to the adventitia of the blood vessels. In the zone of glial cells and fibres left attached to the vessel some cells look normal, some are a little vacuolated, while others are rounded, detached from the rest of the tissue, and are full of fat globules.

A few of the foamy cells also contain clumps of minute yellowish-brown granules of pigment, and occasional cells are uniformly filled with such pigment. The nature and origin of the pigment is not clear. It is a lipochrome (Scharlach R; osmic acid), and gives negative reactions for iron (Prussian blue reaction) and lead (39). In older cases, after the fluid exudate has disappeared, these pigmented cells about the blood vessels in the white matter and meninges persist and may be quite numerous (Case 18). Both foamy cells filled with fat and pigmented cells are occasionally found in the gray matter about vessels which extend from the surface into the central white matter.

Nerve Cells. Various changes are found in the nerve cells. Since the number of abnormal cells and the degree of damage vary in different cases and in different areas of a given brain, it is necessary to examine sections from many parts of the brain in each case.

There is, first, mechanical displacement of the cells by the serous exudate. A few cells in localized areas may be displaced by perivascular rings of exudate and by clusters of coagulated drops of older exudate, but the arrangement of many nerve cells is disordered in the

larger fields of the gray matter which are diffusely saturated with serous fluid.

Nerve cells in areas filled with coagulated exudate have vague outlines, and the cytoplasm is not sharply demarcated from the surrounding tissue. The cytoplasm is more basophilic than normal, and distinct Nissl granules can scarcely be made out. The whole cell body stains diffusely with Nissl stains (gallocyanin, thionin, cresyl violet). The nuclei are more basophilic than normal, nearly pyknotic in appearance, and the nucleoli are indistinct.

Many of the nerve cells in the torn spongy areas from which exudate escapes resemble the cells in areas filled with coagulated exudate. In the vacuolated areas the nerve cells tend to be smaller than normal, however, and many are represented by altered nuclei and very thin rings of cytoplasm, the whole cell lying at one edge of a large empty space. In the areas which are extremely porous many completely necrotic cells are usually found. Such changes may be seen in any part of the gray matter, including Ammon's horn.

Necrotic cells are scattered irregularly in all of the cases. They are very numerous in many, and some are found in practically every microscopical section in most cases. Necrotic cells are much smaller than normal. They are sharply outlined and the cytoplasm is homogeneous, hyaline, and stains bright pink with eosin. The nuclei are pyknotic, solid black, and may be fragmented. Often they are found triangular in shape, like the cell itself. Some of the necrotic cells may be surrounded by several neuroglia cells, the so-called neuronophagia, but numerous necrotic nerve cells may be found without any increase in the surrounding neuroglia.

Most of the changes in the nerve cells seem to be related to the vascular lesions and consequent presence of exudate in the tissues. It is not evident as yet that lead acts directly on the cells.

Foci of Necrosis. Small circumscribed foci of necrosis in the cerebrum were found in 12 of the 22 cases. In some cases they were seen only in the gray matter, in others only in the white matter, and in 5 cases they were present in both the gray and white matter. In one of the cases (No. 20) haemorrhagic lesions of this type are very numerous and readily visible in the gross specimen. The lesions vary in size from about 40 to 200 micra in diameter, and are characterized by

pyknosis and fragmentation of the cells and granular disintegration of the fibres. There is usually a ring of multiplying glial cells, some in mitosis, about the necrotic foci, and the smaller ones may be diffusely infiltrated by glial cells. In addition to the peripheral rings of neuroglia there may be circular haemorrhages about some of the necrotic areas, and in some instances more or less diffuse infiltration of the necrotic tissue by red blood cells and neuroglia.

The small areas of necrosis are apparently minute infarcts. In the cases which contain many there are also numerous necrotic capillary segments and capillary thrombi; and often a necrotic capillary segment occluded by a thrombus is found within or at the margin of the necrotic tissue. The demonstration of a causal relationship between capillary thrombi and each of the foci of necrosis could only be determined by cutting many serial sections.

Haemorrhages. Three types of haemorrhage have been found in this series of cases. Minute rings of blood surrounding arterioles and capillaries are present in the gray and white matter of most of the cases. They are usually more numerous in the white matter than in the gray cortex and are variable in size, some measuring 60 x 120 micra. The perivascular haemorrhages are independent of the rings of serous exudate which usually contain no red blood cells whatsoever. In some cases few perivascular haemorrhages are found, while in others they are numerous. No apparent relation exists, however, between the occurrence of convulsions and the number of haemorrhages. This is illustrated by Case 21 in which there were no convulsions and perivascular haemorrhages are as numerous as in other cases characterized clinically by the occurrence of many convulsions.

Haemorrhages of a second variety are shown by the circular rings of blood which are frequently found about the periphery of small foci of necrotic tissue described above. Larger haemorrhages have rarely been observed in this group of cases. In one case (No. 12) a confluent group of haemorrhages 5 to 6 mm. in diameter was found in the white matter, and in another (No. 18) several small thin microscopic films of blood were found under the meninges.

THE CEREBELLUM

The cerebellum is intensely affected in lead encephalitis, and the same variety of lesions occurs in both cerebellum and cerebral

hemispheres. In the cerebellum, too, the lesions are patchy in distribution, and so it is important to examine sections from many areas. In this series from 4 to 12 blocks of the cerebellum were cut in 12 cases. In six of the earlier cases the cerebellum was not examined microscopically, and in four the microscopical sections were made from single blocks of tissue.

It is not necessary to describe again in detail the changes in the capillaries and arterioles, the old and fresh exudate about the vessels and far out in the tissues, the disordered architecture, and the necrotic cells and tissue, since these are similar in the cerebellum and cerebral hemispheres. On account of the peculiar architecture of the cerebellum, however, there are certain particular lesions which should be described.

It is well known that cells of the marginal embryonic stratum, nervous elements resembling the cells of the granular layer, persist on the surface of the molecular layer just under the meninges of the cerebellum for several years after birth (40). In the cases of lead encephalitis in which this layer of cells persists, the serous exudate about the capillaries and in spongy patches in the surface of the molecular layer dislodges many of the cells and forces them out into the meshes of the meninges, just as neuroglia cells are forced into the meninges from the molecular layer of the cerebral cortex. The cells found free in the meshes of the meninges of the cerebellum consist almost entirely of small round cells from the marginal embryonic stratum, and it is evident that they too may be found in the spinal fluid taken for clinical examination.

In the cerebellum, lesions in the molecular layer are numerous and conspicuous in most of the cases. Damaged capillaries, capillary thrombi, perivascular little foci of necrosis, haemorrhages, and thin films of serous exudate about many capillaries, are commonly found. About many capillaries, for some distance, often stretching from near the meninges to the Purkinje layer, the tissue is very coarse and porous. Some of the spaces may contain coagulated serous exudate. The nerve fibres are stretched and separated, some have disappeared, and a good many new glial cells and fibres are found loosely arranged in the spongy perivascular areas.

The large nerve cells in the Purkinje layer are especially subject to damage and are found vacuolated and even necrotic. In most cases

many of them have disappeared. The whole Purkinje cell layer is stretched and spongy, and in some of the cases it is filled here and there with coagulated serous exudate. With disappearance of the nerve cells, their dendrites in the molecular layer disappear, and also the axones of basket cells which normally terminate about the Purkinje cells.

In five cases there are several extremely and diffusely atrophied folia. In these five cases from 4 to 8 blocks of the cerebellum were cut, and it is evident that the recognition of the extreme changes in isolated scattered folia was a matter of chance depending on the number of blocks cut. The diffusely affected folia are very small, and each layer is thin. Most of the Purkinje cells and many of the granular cells have disappeared. Many dendrites of Purkinje cells are missing, so that the molecular layers, composed principally of these fibers, become very coarse-meshed, and new glial cells and fibres are found both in the molecular and granular layers. Thick cuffs of lymphocytes may be found about small blood vessels in the meninges over these extremely altered folia, and in one case there are clumps of minute basophilic granules in the molecular layer which suggest fragments of necrotic calcified fibres.

Noteworthy changes occur in the dentate nucleus, where a good many necrotic nerve cells are usually found, some surrounded by clusters of glial cells. In some cases there are little rosettes, nodules which may measure 50 micra in diameter, composed of 30 to 40 glial cells. In some parts of the dentate nucleus more widespread loss of nerve cells may be found and a corresponding more or less diffuse infiltration with glial cells. Changes in the capillaries are conspicuous, and there are thin rings and small drops of fluid coagulated about many capillaries. The tissue about a good many capillaries is coarse and porous, the fibers stretched and distorted, and there is pericapillary infiltration with neuroglia. Where capillary thrombi occur, small round foci of necrosis may result, with peripheral rings of red blood cells and glial cells.

In the white matter of the cerebellum wide pools of perivascular serous exudate are often found, and other large areas from which much of the tissue has disappeared, leaving a coarse network of stretched, torn and necrotic fibres. Perivascular foamy fat-laden

cells and pigmented cells are found in the cerebellum as in the cerebral cortex.

THE BASAL NUCLEI, MESENCEPHALON, PONS, MEDULLA AND SPINAL CORD

In this series the same variety of lesions and changes of identical character are found throughout the entire central nervous system. In the basal nuclei and mesencephalon, the pons, medulla and spinal cord, however, the intensity of injury is less marked; the quantity of exudate is less abundant; and the distortion of architecture less evident than in the cerebral hemispheres and cerebellum. But it is important to point out that microscopical examination of numerous sections of the basal nuclei, brain stem, and spinal cord shows small lesions of one kind or another at nearly all levels and in many of the sections. Actually there are very numerous widely scattered small lesions, although the changes in a single microscopical section may appear to be slight (Table II).

To summarize briefly, the lesions are more numerous in the grey matter than in the fibre tracts, and they are less evident in the spinal cord than elsewhere. Swelling and multiplication of nuclei in the walls of capillaries and adventitia of arterioles, necrosis of capillary segments and capillary thrombi are found on careful examination of the sections. Likewise, films and small drops of exudate coagulated about scattered capillaries are fairly numerous, and wider pools of serous exudate are seen about occasional arterioles. There are large fields diffusely saturated with serous exudate in the putamen in two cases and in the caudate nucleus in three. Serous fluid is rarely found in the meninges. Older drops of perivascular exudate showing various degrees of basophilia were encountered, usually in the caudate nucleus, corpus striatum and thalamus, in six of the acute cases, excluding the three cases of longer duration already mentioned. In some of these six cases similar basophilic areas resembling calcium were found in the walls of small blood vessels.

Spongy porous areas of distorted tissue, damaged glial cells and proliferating neuroglia are likely to be seen in the superficial molecular layer of neuroglia of the mesencephalon and brain stem; and there is a similar distortion of the architecture about many capillaries and arterioles, together with serous exudate in some of the porous peri-

TABLE II

Necrotic Nerve Cells, and Foci of Necrotic Tissue with Glial Reaction in Basal Nuclei, Mesencephalon, Pons, Medulla, and Spinal Cord

CASE NO.	NUMBER OF SECTIONS EXAMINED	NECROTIC NERVE CELLS WITH FEW NEUROPHAGOCYTES	FOCI OF NECROTIC TISSUE	NODULES OF NEUROGLIA ABOUT NECROTIC CELLS OR REPLACING NECROTIC TISSUE
1	1	Spinal cord	0	1 in lateral horn of cord
2	4	Spinal cord, nu. cuneatus, inf. olives, sub. nigra, red nu., geniculate body, corpus striatum and thalamus	3 in lateral columns of cord	Numerous in geniculate body and thalamus
3	1	Inferior olive	0	0
4	5	Spinal cord, thalamus, corpus striatum, caudate nucleus	1 in thalamus and 1 in globus pallidus	2 in anterior horn of cord
5	1	Spinal cord	0	0
6	6	Cord, post. colliculi, geniculate body, thalamus, putamen, caudate nucleus	12 in gray matter of medulla at decussation; 2 in thalamus	Several in geniculate body and thalamus
7	3	Cord, nuclei gracilis and cuneatus, post. colliculi, inf. olives	0	1 in pyramidal tract at decussation
8	2	Spinal cord and nuclei pontis	0	0
9	1	Spinal cord	0	0
10	1	Sub. nigra, paraventricular nuclei, and thalamus	0	Several in thalamus
11	17	Cord, inf. olive, nuclei pontis, gracilis and cuneatus, inf colliculus, thalamus, corpus striatum, and caudate nucleus	Several in inferior olives	1 in cord; several in inf. olive, nuclei gracilis and cuneatus, and in thalamus
12	11	Cord, nuclei gracilis and cuneatus, inf. olive, nuclei pontis, the colliculi, hypothal. nu., thalamus, putamen, and caudate nu.	1 in thalamus (infarct of 7 mm.). Several in nu. cuneatus	Several in the inferior olives.
13	15	Cord, nu. cuneatus, nuclei of nerves 5, 6, 7; the olives, nuclei pontis, sub. ferruginea, red nu., thalamus, caudate nu., and corpus striatum	1 in geniculate body	1 in dorsal column of cord. Several in geniculate body. Many in the inferior olives

14	20	Cord, nu. of Schwalbe, nu. of nerves 7 and 12, inf. olives, nu. pontis, hypothalamic nu., geniculate body, and thalamus	1 in thalamus (infarct of 4 mm.)	1 in gray matter of lumbar cord. Several in nu. of Schwalbe, 1 in nu. of tract. solitarius, several in geniculate body, numerous in thalamus
15	16	Spinal cord, nuclei gracilis and cuneatus, inf. olives, nu. of several cr. nerves, nuclei pontis, the colliculi, red nu., sub. nigra, and thalamus	1 in triangular nu. vest. nerve	1 in nuclei pontis; 1 in sup. colliculus, several in thalamus
16	15	Cord, nuclei gracilis and cuneatus, inf. olives, triangu. nu., vestib. nerve, nu. of N. 12, nuclei pontis, the colliculi, sub. nigra and ferruginea, red nu., and thalamus.	0	2 in nucleus gracilis
17	19	Cord, nu. gracilis and cuneatus, the olives, nu. lateralis, nuclei pontis, inf. colliculi, sub. nigra, red and hypothal. nuclei, thalamus, corpus striatum, and caudate nucleus. Nuclei of Schwalbe and of cranial nerves 4, 5, 7, 8, and 12	Nucleus of Schwalbe (1), inferior and dorsal acces. olives (several), thalamus (several)	Ant. horn of cord (several), nu. cuneatus (several), inf. olive (many), restiform body (1), reticular sub. of pons (1), nu. of N. 4 (1), hypothal. nu. (several)
18	22	Cord, nuclei gracilis and cuneatus, nu. of N. 12, inf. olives, thalamus, corpus striatum	Nu. cuneatus (1), motor nu. N. 5 (1), nu. of sp. br. of N. 5 (1), brachium conjunctivum (1) thalamus (1)	2 in nu. of N. 3, several in inf. olives, 1 in nu. of N. 12, and 2 in reticular sub. of pons
19	18	Cord, nuclei gracilis and cuneatus, nuclei of nerves 4, 5, 7, 8, and 12; nu. of Schwalbe, the olives, inf. colliculi, nuclei pontis, thalamus, caudate nucleus, corpus striatum	Several in ant. horns of cord at decussation	Ant. horn of cord (1), nuclei gracilis and cuneatus (several), nu. of N. 8 (several), restiform body (1), nuclei pontis (1), nu. of Schwalbe (2), ret. sub. of pons (1), nu. N. 4 (1), inf. olive (several), globus pallidus (1), thalamus (1)
20	15	Cord. inf. olives, inf. colliculi, thalamus, caudate nucleus	Cord at decussation (2), nu. of N. 8 (several), inf. olives (several), sup. olive (1), fibres of ventral pons (2), nu. of N. 12 (several), inf. colliculus (1); red and hypothal. nu., geniculate body, thalamus, corp. striatum (many)	Sup. olive (1), retic. sub. of pons (1), thalamus (few)
21	12	Cord, nuclei gracilis and cuneatus, nu. sp. br. N. 5, nu. N. 6, the olives, nuclei pontis, sub. ferruginea, hypothal. nu., thalamus, corpus striatum, caudate nucleus	Nuclei gracilis and cuneatus (several)	Reticular sub. of medulla (3), inf. olives (several), reticular sub. of pons (several), hypothal. nu. (several)
22	19	Cord, nu. sp. br. N. 5, nuclei gracilis and cuneatus, nuclei of nerves 6, 7, and 12; sup. and inf. olives, sub. ferruginea, thalamus	Reticular sub. at decussation (1)	Pyramidal tract at decussation (1), nu. cuneatus (1), inf. olives (few)

vascular areas. Pigmented cells and fat-laden cells about blood vessels are found at various levels, and a few small perivascular haemorrhages in the basal nuclei, brain stem, and spinal cord in eighteen of the cases.

Necrotic nerve cells, focal areas of necrotic tissue, and older circumscribed nodules of neuroglia replacing normal structures form the most conspicuous lesions, although regularly associated with vascular changes and evidence of exudate in the tissue. The numbers of these lesions and their distribution in the present series may be seen in Table II.

Necrotic nerve cells are scattered in small numbers in many nuclei (Column 1, Table II). In most instances few necrotic cells are found in a given microscopical section. Several glial cells are usually found immediately about the necrotic nerve cells, but in the inferior olives, the geniculate bodies, and in the thalamus it is not uncommon to see scattered solitary necrotic cells with bright pink hyaline cytoplasm, no Nissl granules, and pyknotic nuclei.

In the spinal cord the smaller nerve cells of the lateral horns seem more susceptible to injury than others, and in general large cells like those in the anterior horns, in the substantia nigra, and locus caeruleus, are apparently the more resistant. In the spinal cord and in the nuclei of gracilis and cuneatus, in nuclei of cranial nerves and in the nuclei pontis, in the colliculi, red nucleus, putamen and caudate nucleus some of the nerve cells undergo karyolysis and fade away. The cytoplasm of the injured cells disappears, while their nuclei are left better preserved, surrounded by neurophagocytes.

The foci of necrotic tissue resemble those in the cerebral hemispheres and cerebellum. They are associated with marked changes in closely related capillaries, and in many instances they contain necrotic capillary segments and capillary thrombi. Most of the areas are more or less rounded and vary from 40 to 80 micra in diameter. Some are 100 to 200 micra in size, and in two cases small infarcts, 4 and 7 mm. in diameter, were found in the thalamus, each surrounded by acute inflammatory exudate (Nos. 12 and 14). The smaller foci of necrosis usually show a ring of glial cells and red blood cells in a peripheral zone of spongy vacuolated tissue, and they may contain recognizable shadows or nuclei of necrotic nerve cells.

The changes in nerve cells and in small foci of the tissue described

above have the appearance of fresh lesions. Similar lesions, which are evidently older, are found in most of the cases and are listed in Columns 3 of Table II. They correspond in size and distribution to the fresher lesions from which they differ chiefly in containing more abundant, and more mature neuroglia. The older lesions vary from 25 to 200 micra in diameter, although most measure 40 to 80 micra. There are a good many of large size, however, 120 to 160 micra in longest diameter, and in one case a nodule of fibrous tissue and neuroglia measuring 250 x 400 micra was found in one of the dorsal columns of the spinal cord (Case No. 13).

Listed among the older lesions are, first, single necrotic nerve cells or fragments surrounded by numerous closely packed glial cells forming nodular rosettes. They are found especially in the inferior olives, geniculate bodies and thalamus. Secondly, there are many small nodules of neuroglial tissue composed of nuclei and fibres which replace normal tissue. These occur in both gray matter and fibre tracts. The glial nuclei are loosely arranged, not closely packed together, in the little nodules of fibres. They are most numerous in the inferior olives, and are probably formed by the growth of neuroglia in foci of tissue once necrotic, lesions like the fresh foci of necrosis described above.

THE MENINGES, CHOROID PLEXUS, RETINA AND OPTIC NERVES, PINEAL GLAND AND HYPOPHYSIS

The Meninges. No especial primary lesions of the meninges have been found in any of the cases in this series and none of the microscopical lesions confirm the suggestion that in lead poisoning there is a primary meningopathy (2). The changes which do occur concern the blood vessels, and are like the vascular lesions in the gray and white matter. They are readiiy seen in small branches which penetrate the molecular layer from larger vessels above in the meninges. These arterioles and capillaries show dilatation and narrowing, swelling and multiplication of nuclei, and necrotic pyknotic nuclei as observed in the gray and central white matter. Capillary thrombi in meningeal vessels, however, have rarely been found in any of the cases.

The outpouring of serous exudate produces the spongy patches in the molecular layer as already described, and some of the exudate may

remain coagulated about the vessels and in the tissue. The escape of fluid from the vessels pushes the inner layer of the pia mater up and tears many of its fibres from their moorings. There is some evidence, too, of slight proliferation of cells in the displaced and torn meninges; and, as already described, a good many damaged and necrotic glial cells and cells of the marginal embryonic stratum of the cerebellum are forced from the surface of the molecular layer and come to lie free in the meshes of the pia mater. Besides these cells, in a few cases very small numbers of polymorphonuclear leucocytes have been found in the meninges, and there may be small lymphocytes about vessels in the meninges overlying the localized folia in the cerebellum which are extremely altered as described above. In the majority of the cases, however, there is no evidence of any diffuse leucocytic reaction in the meninges.

In addition to the exudate about the meningeal vessels penetrating the molecular layer, in most of the cases there is evidence of abundant serous fluid about small vessels between the two layers of the pia mater. The exudate is usually found in patches on the surface of convolutions and deeper in the sulci. In some cases the sections made show little fluid, but in many cases it is very abundant. It is identical in appearance with serum within the blood vessels coagulated by the fixing fluid, and apparently escapes from damaged blood vessels in the meninges. It is therefore not abnormal cerebrospinal fluid, since it is not a secretion from the choroid plexus, but rather an exudate.

The Choroid Plexus. Microscopical sections of the choroid plexus of fifteen of the cases were examined, and no definite lesions in the epithelial cells were recognized. In all of the cases examined, however, there is a patchy separation of the epithelium from the underlying blood vessels, and vacuolization of the stroma. In three cases narrow rings of serous exudate remain coagulated about very few vessels. Demonstrable changes in the walls of the blood vessels are slight, but there is some swelling of the nuclei in the walls of some of the capillaries and arterioles.

There is no microscopical evidence therefore that in lead encephalitis the cerebrospinal fluid secreted by the choroid plexus is either increased in amount or abnormal in composition. The changes in the blood vessels of the brain and meninges, and the abundant serous

fluid in both locations show clearly that the increased intracranial and intracerebral pressure and the protein found in the spinal fluid clinically result from widespread vascular damage and consequent outpouring of serous inflammatory exudate which escapes principally from the blood vessels of the brain and meninges.

The Retina and Optic Nerves. The retina, optic discs and nerves were examined microscopically in five cases. In each instance there are spongy, vacuolated patches, especially along margins of capillaries, in the nerve, optic disc, and in the nerve fibre layer of the retina. In three cases patches of serous fluid were coagulated on the surface of the nerve fibre layer.

Microscopical sections of the optic chiasm and nerves were made in eight other cases. Five of these show spongy patches about capillaries. In another case there are, in addition, occasional perivascular rings of coagulated serous exudate, and small perivascular haemorrhages occur in three cases.

The Pineal Gland. In eight of the cases single blocks were made from the pineal gland at autopsy and one microscopical section was prepared from each, stained with haematoxylin and eosin. In most cases the gland was torn in removal, and the sections are somewhat faulty. Three, however, show irregular gaps in the tissue, each filled with serous fluid, and in several of the cases there is some irregularity and increase in the size of some of the nuclei. It seems probable that further study of material prepared more carefully would show more definite and more numerous changes in the pineal gland.

The Hypophysis. The hypophysis was examined microscopically in seventeen of the cases. Changes which were slight in most instances were found in the anterior lobe in twelve cases. In nine there is serous exudate about some of the capillaries. In most of these only a little perivascular fluid is found about a few vessels. In one case (No. 22) the exudate is quite abundant in patches in the central part of the anterior lobe, and produces some tearing of the tissue and displacement of the cells.

A few irregularly scattered necrotic cells and groups of two to five necrotic cells are found in the anterior lobe of seven cases; and in two others there are larger microscopical foci of necrosis. Small haemorrhages are present in two cases. In a good many there are occasional

cells in the anterior lobe with greatly enlarged hyperchromatic or pale vesicular nuclei.

PERSISTENT LESIONS AND FUNCTIONAL DISTURBANCES

Children may recover from lead encephalitis and live on with a variety of permanent functional disorders which will vary in character with the location and intensity of the original lesions in the brain. McKhann described a case in which blindness, spastic left hemiparesis, and occasional convulsions were present three years after the acute encephalitis occurred; and a ventriculogram showed evidence of atrophy on the right side of the brain (13). In the present group of 22 cases there are three somewhat similar examples.

In one case (No. 5) a week after the original convulsions the child showed generalized spasticity, spastic paralysis on the left, constant purposeless movements of the head, face, tongue and right arm; and there was evident disturbance of mentality. These signs persisted and a month later the child died with convulsions. Several atrophied cerebral convolutions were found on each side of the brain at autopsy. The microscopical sections show fresh vascular changes and fresh exudate together with older lesions. There are perivascular collections of old exudate with basophilic changes and iron content; and in the gray matter many nerve cells are atrophied and whole fields of cells concentrated together from loss and collapse of the tissue.

In a second case (No. 7), for about a year there were periods of abdominal pain, constipation, vomiting, and crying spells. Peripheral neuritis finally developed, with flaccid paralysis of all the extremities, paralysis of the trunk and diaphragm, and almost complete loss of sensation. For several hours before death there was high fever and coma, together with convulsive movements of the muscles of the neck and face. Microscopically, both fresh and old lesions are found in the brain and also the lesions of peripheral neuritis. Many large microscopical fields in the cortex show extensive destruction and a loss of tissue, and there is abundant old perivascular exudate. Few blocks of the brain were prepared, and the possible relation between the lesions in the brain and the loss of sensation must remain in doubt.

In the third case (No. 18), three years elapsed between the original convulsions and the final attack of lead encephalitis. Examination

made two years after the first attack showed quite marked mental retardation, but no other definite functional disorders were recognized. The microscopical sections of the brain show fresh lesions and exudate, and very abundant old basophilic perivascular exudate scattered everywhere in the cerebral cortex. Old areas of perivascular encephalomalacia and more diffuse loss of tissue in the central white matter of some convolutions are evident; and in the cerebellum there are extensive old lesions.

ON THE PATHOGENESIS OF THE VASCULAR CHANGES AND THE EXUDATE

Experimental lead encephalitis is readily produced in laboratory animals, and the lesions found by various writers have been reported. A good review is that of Farraro and Hernandez (41). In their own experimental animals these authors found lesions in blood vessels, nerve cells and fibres, and in neuroglia, but no fluid exudate was described. Weller and Christensen (42) reported the occurrence of oedema of the brain in experimental lead encephalitis, describing spongy vacuolated areas in the tissue as oedema. We have found no experimental reports, however, in which the presence of exudate coagulated in the tissues has been recognized.

It seems evident from the familiar swollen appearance of the brain which has been often described in the literature, and from the present series of cases in which there is abundant serous exudate about blood vessels and diffusely infiltrating the brain, that vascular damage and exudate of fluid which may coagulate in the brain, or partly dissolve in the fixative, are characteristic of acute lead encephalitis. The spongy porous changes pictured by Weller and Christensen (42) in the brain of the experimental animal indicate that the experimental disease is similar in these respects to the disease in man.

Lead encephalitis is said to be purely a "degenerative" disease without evidence of inflammation (41). But as a matter of fact, the vascular changes, the haemorrhages, and the exudate of serous fluid are inflammatory lesions of a particular type. They differ in intensity from more familiar examples such as sero-fibrino-purulent peritonitis and meningitis.

It appears, then, that the lesions in the brain are for the most part dependent on vascular damage and the collection of exudate. But

the precise relation between lead in the tissues and the pathogenesis of the vascular phenomena is not clear. It seems likely, however, that the usual occurrence of lead encephalitis in children during the warm months of summer and fall, and the presence of fever in most cases, may be significant factors in initiating the changes in the cerebral blood vessels which are followed by widespread serous exudate and tearing of tissue. The question requires further investigation, but at this point experiments in support of this view may be mentioned briefly.

Twenty-four rabbits were given daily subcutaneous injections of 1 cc. of basic lead acetate for 7 weeks without exhibiting any signs of encephalitis. Eight of them were then placed in the incubator at 37°C., which produced an elevation of 3 or 4°C. in the temperature of the animals. Four of the rabbits died within 24 hours; the others lived for 38, 53, 60 and 102 hours, respectively. The controls injected with lead and kept at room temperature were killed and autopsied. Normal controls were killed after living for two weeks in the incubator at 37°C., with a temperature 3° to 4° above normal. The rabbits which were injected with lead and placed in the incubator all developed pulmonary oedema, and microscopical sections show serous exudate about capillaries in the meninges and molecular layer of the cortex, spongy porous areas in the surface of the molecular layer, and upward displacement of the inner layer of the pia mater—lesions which are characteristic of lead encephalitis in children. These lesions were not found in either set of control animals.

The experiment and the fact that acute lead encephalitis usually occurs in the summer and fall suggest that lead acts on the blood vessels of the brain in such a way that they become more permeable than normal when they are dilated by agents such as rising atmospheric temperature and fever.

SUMMARY

In acute lead encephalitis the brain is swollen, and may be hyperaemic or pale. When blocks of fresh tissue are placed in alcohol, a milky precipitate is formed by plasma protein in the exudate which escapes.

Lesions are found throughout the entire central nervous system.

They are most abundant in the cerebral hemispheres and cerebellum. All of the changes are patchy in distribution, but examination of many sections shows the presence of numerous lesions.

The microscopical changes are those of a serous inflammation. Vascular lesions are found, including capillary necrosis and thrombi, together with abundant exudate, tissue damage, and evidence of repair. Most of the injury to the nervous tissue seems dependent on the accumulation of exudate.

The exudate is composed of serous fluid, usually without fibrin. A part is coagulated in the brain by the formalin; some is older, inspissated in appearance, and coagulated in the tissue before death; and a portion is extracted by the fixing and dehydrating agents.

The freshly fixed serous exudate is found about blood vessels and in the meninges in all cases; and in many cases large fields of tissue in many convolutions are diffusely saturated with the exudate.

The older inspissated exudate is found especially about capillaries in the gray matter in the form of small droplets. After periods of weeks and years they become basophilic, accumulate iron, and stain like calcium. The mechanism by which this exudate is coagulated remains obscure, and the clotting of fibrin is not concerned. Similar basophilic areas are found in the walls of blood vessels after elapse of months and years.

The fresh serous exudate and the older droplets cause distortion of the architecture of the brain, depending on the location and quantity of the fluid. Fields in the gray and white matter diffusely saturated with exudate contain many damaged and necrotic nerve and glial cells, and there is marked tearing and necrosis of fibres. The necrotic nerve cells may be surrounded by several glial neurophagocytes.

The portion of the exudate which escapes in the fixing and dehydrating fluids leaves stretched and torn areas in the tissue like those in which coagulated fluid remains. Large confluent spongy areas are found in the gray matter and in the central apical white matter; and there are certain other characteristic zones and foci which are especially coarse and porous.

Very coarse torn spongy patches regularly occur in the superficial part of the molecular layer of the brain and cerebellum. The exudation of fluid into these areas tears and pushes up the inner layer of

the pia mater, and scatters necrotic neuroglia cells and cells of the marginal embryonic stratum of the cerebellum into the meshes of the meninges. These glial cells and embryonic cells constitute the majority of the cells free in the meninges and they appear also, no doubt, in the spinal fluid.

Especially coarse spongy tissue is also found in a narrow zone at the junction of the gray and white matter of many convolutions, and there are similar circumscribed foci about arterioles and capillaries. Some of the spaces in the vacuolated zones and foci generally contain coagulated serous exudate, although most are empty.

Small perivascular haemorrhages in variable numbers occur in most cases, and small focal areas of necrosis may be found in any part of the brain, usually in association with necrotic capillary segments or capillary thrombi. They may be surrounded or diffusely infiltrated by haemorrhage and glial cells. Damaged and necrotic glial cells and new astrocytes are found, especially in the spongy porous molecular layer, in the apical central white matter and about arterioles in the white matter.

Lesions of similar character are scattered in the cerebellum and are especially evident in the molecular layer, the Purkinje layer, and in the dentate nucleus. On making sections from many parts of the cerebellum, extreme changes affecting whole folia and single lobules are likely to be found.

In the basal nuclei, brain stem, pons, medulla and spinal cord, the lesions are small, few in number in a given section, and scattered at wide intervals. In these structures small rosettes of glial cells about necrotic nerve cells, foci of necrotic tissue, and nodules of neuroglial cells and fibres replacing the damaged tissue, are conspicuous. Slight changes were found in this series of cases in the choroid plexuses, the retina and optic nerves, pineal gland, and hypophysis.

In patients who recover after the initial convulsions, functional disorders varying from mental retardation to spastic paralysis may be expected, depending on the intensity and location of the injuries. Microscopically, there is a corresponding loss of tissue in the gray and white matter of the brain and cerebellum. Remnants of old coagulated exudate are found, basophilic in appearance like calcium, and basophilic plaques in the walls of blood vessels.

Fever and marked leucocytosis were present in most of the cases in this series, and the signs of encephalitis appeared during the hot months of summer and fall in 19 of the 22 cases. In another patient, dying in January, the encephalitis appeared in association with widespread lobular pneumonia caused by the Type II Pneumococcus. It is suggested that factors which cause vasodilatation, such as fever and the temperature of summer weather, may be important in precipitating the lesions in the brain. Experimental evidence is cited in support of this idea.

APPENDIX I. USEFUL STAINS FOR THE DEMONSTRATION OF COAGULATED SEROUS EXUDATE IN THE BRAIN

The exudate is eosinophilic like blood serum, and the perivascular accumulations are readily seen in ordinary sections stained with haematoxylin and eosin. Large areas in the gray and white matter diffusely saturated with the exudate are stained more intensely with eosin than other areas, and inspection of the stained sections with the naked eye will show the deeply stained, dark red areas in sharp contrast to the paler porous tissue which contains less exudate. Under the microscope one can see the pink-stained fluid coagulated between the fibres in the white matter, and areas in the gray matter saturated with exudate look very hyalin, homogeneous and smooth.

The precipitated protein in the exudate may be demonstrated by a variety of stains. It appears as black granular material in Weil's myelin-sheath stain (37). Even after the differentiation has been carried too far and the myelin sheaths are no longer stained, much of the exudate remains as a black precipitate. Bodian's silver method (38) for axis cylinders stains the exudate which appears as fine purplish granules.

These methods are unsatisfactory because the contrast between the color of the fluid and that of the tissues may be slight. By the use of safranin and light green the blood serum and the serous exudate are stained red. Areas in the gray and white matter which are not filled with exudate turn green, and by this method the serous red fluid in the vessels, around the vessels, and in the tissues is brought out in sharp contrast against a green background.

Technique

1. Fix thin blocks in formalin. Dehydrate, embed in paraffin and cut sections in the usual way.
2. Remove paraffin with xylol, pass through alcohol, and wash in water.
3. Stain for half an hour at 40° to 50°C. in a saturated aqueous solution of safranin Y.
4. Wash in water and quickly saturate section in 95 per cent alcohol.
5. Differentiate in saturated alcoholic solution of light green. This step

requires care. If the section remains in light green too long, the blood serum, the exudate and all of the tissue, will be stained dark green. Differentiation requires only a few seconds. The section should be dipped quickly in and out of the light green. Proper differentiation is reached when the tissue which does not contain the exudate turns pale green and the areas filled with serous fluid look very dark green *to the naked eye.*

6. Wash in water and examine under the microscope. If necessary, differentiate further.
7. Dehydrate quickly in graded alcohols and xylol.
8. Mount in balsam.

APPENDIX II. CASE REPORTS

Case 1. Autopsy No. 5940. A colored boy, 3 years old. History of pica, malaise for a month, and repeated convulsions for one day. Lead line on gums. Stippled red blood cells. Haemoglobin 60 per cent. *Spinal fluid:* Pandy +, cells 15 per cu.mm. *Temperature:* 99.8° to 101.2°F. *Leukocytes:* 19,000. *Died* in July. Lead line in microscopic sections of ribs. Nuclear inclusion bodies in liver and kidneys.

Case 2. Autopsy No. 7532. A white girl, 2 years old, who ate the paint from window-sills and toys. She was easily frightened and startled and had screaming spells for two months. Vomiting present at times for one month. Coma, nystagmus, and convulsions for a day. *Blood:* Haemoglobin 45 per cent. Stippled and nucleated red blood cells. *Spinal fluid:* Pandy 3+. Cells, 12 per cu.mm. *Temperature:* 100° to 105°F. *Leukocytes:* 58,500. *Died* in June. Slight lobular pneumonia. Lead line in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidney.

Case 3. Autopsy No. 10465. A colored boy, 3 years old, who ate house paint. History of vomiting, strabismus, and convulsions off and on for a week. Lead line on gums. *Blood:* Red blood cells 3,950,000. Stippled red cells. *Spinal fluid:* Pandy +. Cells, 5 per cu.mm. Pressure increased (1+). *Temperature:* 38° to 39.6°C. *Leukocytes:* 15,400. *Died* in July. Lead line in microscopical sections of ribs. Intranuclear inclusion in liver and kidneys.

Case 4. Autopsy No. 10637. A white boy 22 months old, who chewed painted furniture for six months. Later constipation, projectile vomiting, and drowsiness appeared for three weeks. He had convulsions and strabismus for three days. *Blood:* Haemoglobin 50 per cent. Stippled red blood cells. *Temperature:* 37° to 38.8°C. *Leukocytes:* 16,400. *Spinal fluid:* Pandy +. Cells 9 per cu.mm. Pressure increased (4+). *Died* in October. Purulent bronchitis, microscopical lead line in ribs, and nuclear inclusions in liver and kidneys.

Case 5. Autopsy No. 10850. A white boy, 13 months old, who gnawed painted furniture for four months. Had a cold and convulsions with fever (104°) for two days a month before death. The first convulsion appeared after the third of a series of daily injections of "cold" vaccine. Later there was spastic paralysis

on the left, and the head and right arm were in constant motion. He was mentally retarded. Several missing teeth and ulcerated gums. *Blood:* Haemoglobin 54 per cent. Stippled red blood cells. *Spinal fluid:* Negative. *Temperature:* 38° to 42°C. *Leukocytes:* 12,300. *Died* in April. Purulent bronchitis and lobular pneumonia. Microscopical lesions of lead poisoning in ribs, and intranuclear inclusions in liver and kidneys.

Case 6. Autopsy No. 11766. A colored boy, 2 years old, who liked to chew paper, plaster, and clothes. For two weeks he was noisy, fretful and disobedient. Enuresis appeared and a tendency to bite and scratch. Occasionally he vomited, and had nystagmus and convulsions for one day. *Spinal fluid:* Pandy 3+. Cells 66 per cu.mm. Pressure increased (1+). *Temperature:* 98 to 105°F. *Died* in December. Lead line in x-ray and in microscopical sections of ribs. Nuclear inclusions in liver and kidneys.

Case 7. Autopsy No. 12168. A colored girl, 3½ years old. Over a year before death there were several periods of vomiting, abdominal pain, constipation, and crying spells. Later she was seen with house paint on her hands and face and a week afterwards vomited persistently for 3 days. This was followed by ascending paralysis, difficulty in speech and swallowing, and dysphagia. Paralysis of extremities and muscles of lower trunk and diaphragm was complete. Weakness of pharyngeal muscles. Occasional convulsive movements of facial muscles. Complete anesthesia to touch and pain over extremities and trunk. Finally, fever, coma and convulsions of facial muscles for several hours before death. *Spinal fluid:* Negative. *Blood:* Haemoglobin 60 per cent. Stippled red blood cells. *Leukocytes:* 19,500 to 22,000. *Temperature:* 37.6° to 38.4°C. *Died* in September, about six weeks after the onset of symptoms. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. Demyelinization of peripheral nerves.

Case 8. Autopsy No. 13334. A colored boy, 3½ years old. History of vomiting for two days. Coma, brachycardia and convulsions for one day. *Blood:* Haemoglobin 45 per cent. Stippled red cells. *Temperature:* 37.4° to 39°C. Leukocytes: 28,000. Blood lead: 0.1 to 0.2 mgm. per cent. Lead line on gums. *Spinal fluid:* Pandy 3+. Cells, 16 per cu.mm. Pressure increased (1+). *Died* in October. Lead line in x-ray and microscopical sections of ribs. Nuclear inclusions in liver and kidneys.

Case 9. Autopsy No. 13698. A colored boy, 2 years old, who ate plaster, ashes, and paint from window-sills. Had abdominal pain and was constipated. History of vomiting for a month. Comatose for four days and had convulsions for one day. Lead line on gums. *Blood:* Haemoglobin 50 per cent. *Blood lead:* 0.5 to 1.0 mgm. per cent. *Temperature:* 37.4° to 38.4°C. *Leukocytes:* 12,880. *Spinal fluid:* Pandy 2+. Cells 30 per cu.mm. *Died* in June. Lead line in bones (x-ray and microscopical). Intranuclear inclusion bodies in liver and kidneys.

Case 10. Autopsy No. 13726. A colored girl, 2 years old, troubled with vomiting for two months. Convulsions chiefly on left side and nystagmus for two days. *Blood:* Haemoglobin 58 per cent. Stippled and nucleated red cells.

Blood lead: 0.1 mgm. per cent. *Spinal fluid:* Pandy 4+. Cells 45 per cu.mm. Pressure increased (2+). *Temperature:* 38.6° to 41°C. *Leukocytes:* 26,350. *Died* in July. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys.

Case 11. Autopsy No. 13795. A colored girl, 2 years old, who ate the paint from her dolls for 2 months. Abdominal pain, constipation and vomiting present for two weeks, and convulsions for a day. *Temperature:* 38° to 40.6°C. *Leukocytes:* 25,500. *Haemoglobin:* 78 per cent. *Blood lead:* 0.5 mgm. per cent. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. *Spinal fluid:* Pandy 3+. Cells, 6 per cu.mm. Pressure increased (2+). *Died* in August.

Case 12. Autopsy No. 13830. A colored girl, 3 years old, who sucked painted toys. History of abdominal pain and vomiting for one month, and long period of crying. Stuporous, with spontaneous motion of head and hands, and right-sided convulsions for one day. Gasping respirations. *Temperature:* 35.4° to 40.2°C. *Leukocytes:* 39,000. *Blood:* Haemoglobin 48 per cent. Stippled and nucleated red blood cells. *Blood lead:* 0.5 to 1.0 mgm. per cent. Lead line in x-ray and in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. *Spinal fluid:* Pandy 4+. Cells, 11 per cu.mm. Pressure increased (2+). *Died* in September.

Case 13. Autopsy No. 14057. A colored boy, 7 years old. Chewed crayon and chalk. Was drowsy for five weeks and had pain in abdomen and back of head. Vomited at times for four weeks. Two days before death he fell twice on the street and was unconscious for a few minutes. He later became comatose and had convulsions. *Temperature:* 37.4° to 39.5°C. *Leukocytes:* 38,800. *Blood:* Red cells 3,720,000. Normoblasts and stippled red cells in blood smears. *Blood lead:* 0.5 mgm. per cent. Lead line on gums. Lead line in x-ray and in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys. Widespread bilateral lobular pneumonia (pneumococcus type II). *Spinal fluid:* Pandy 4+. Cells 25 per cu.mm. Pressure 600 mm. of water. *Died* in January.

Case 14. Autopsy No. 14287. A colored girl 3 years old. History of pica. Vomiting, headache, and drowiness for five weeks. Coma, nystagmus and convulsions for one day. Tachycardia, extrasystoles and elevated blood pressure. *Temperature:* 36 to 40.6°C. *Leukocytes:* 25,700. *Blood:* Haemoglobin 62 per cent. Stippled red blood cells. *Blood lead:* 0.5 mgm. per cent. Lead line in x-ray and microscopical section of ribs. Intranuclear inclusion bodies in liver and kidneys. *Spinal fluid:* Pandy 2+. Cells 25 per cu.mm. Pressure increased. *Died* in June.

Case 15. Autopsy No. 14307. A colored boy, 18 months old, who ate flakes of dry paint from the walls. Had anorexia and was fretful for six weeks. Vomited for a week. Cried almost constantly and held hands to head and abdomen for four days. Convulsions for one day. *Spinal fluid:* Pandy 2+. Cells, 15 per cu.mm. *Blood:* Haemoglobin 50 per cent. *Blood lead:* 0.5 to 1.0 mgm. per cent.

Temperature: 37.4 to 39°C. *Leukocytes:* 8,200. *Died* in July. Lead line in bones (x-ray and microscopical). Intranuclear inclusion bodies in liver and kidneys.

Case 16. Autopsy No. 14336. A colored boy, 19 months old, who ate plaster and was constipated for 2 or 3 months. He was fretful and restless, and lost appetite and weight. For a week he was drowsy and vomited. Had convulsions for one day. Lead line on gums. *Blood:* Haemoglobin 35 per cent. *Blood lead:* 0.2 mgm. per cent. *Spinal fluid:* Pandy 2+. Cells 9 per cu.mm. Pressure increased (1+). *Leukocytes:* 10,000 *Temperature:* 37° to 38.4°C. *Died* in July. Lead line in x-ray and in microscopical sections of ribs. Nuclear inclusion bodies in liver and kidneys. Slight lobular pneumonia in right middle lobe.

Case 17. Autopsy No. 14352. A colored boy, 18 months old, who chewed paint from an icebox and sucked an indelible lead pencil. He was constipated and irritable for two weeks, and vomited at times for a week. Had screaming attacks and convulsions for three to four days. *Spinal fluid:* Pandy 2+. Cells 0. Pressure increased (630 mm. of water). *Blood:* 87 per cent. *Leukocytes:* 8,600. *Temperature:* 37.2° to 40.6°C. *Died* in August. Lead line in x-ray and microscopical sections of ribs. Nuclear inclusion bodies in liver and kidneys.

Case 18. Autopsy No. 14354. A colored girl, 6 years old, poisoned by inhaling fumes from battery casings burned for fuel. She had lead encephalitis with convulsions first in July, three years before death. She recovered, though retarded mentally thereafter. A month before death symptoms reappeared and there were anorexia, cough and fever. One week before death she had a single convulsion, and vomited almost daily afterwards. There were frequent violent convulsions for sixteen hours before death. Lead line on gums. *Spinal fluid:* Pandy 3+. Cells 11 per cu.mm. *Blood:* Haemoglobin 75 per cent. Blood lead elevated for three years (0.2 to 0.5 mgm. per cent). *Temperature:* 38.6° to 40°C. *Leukocytes:* 29,000. *Died* in August. Slight lobular pneumonia. Lead line in x-ray of bones three years ago, at intervals afterwards, and on final admission. Lead line in microscopical sections of ribs. Intranuclear inclusion bodies in liver and a few in kidneys.

Case 19. Autopsy No. 14370. A colored girl, 2½ years old, with a history of pica. Vomiting for a week and convulsions for one day. Lead line on gums. *Spinal fluid:* Pandy 2+. Cells 11 per cu.mm. Pressure increased. *Blood:* Stippled and nucleated red blood cells. Haemoglobin 65 per cent. *Blood lead:* 0.2 to 0.5 mgm. per cent. *Leukocytes:* 24,500. *Temperature:* 39° to 41°C. *Died* in August. Lead line in bones on fluoroscopic examination and in microscopical sections. Intranuclear inclusion bodies in liver and kidneys.

Case 20. Autopsy No. 14849. A white girl, 3 years old, who gnawed painted furniture for 18 months. History of vomiting for three months. She was irritable, nervous, cranky and lethargic for a month. Drowsiness and coma appeared during the last two days of life, and finally convulsions. *Spinal fluid:* Pandy 2+. Cells 11 per cu.mm. *Blood:* Haemoglobin 76 per cent. Stippled red cells. *Blood lead:* 0.55 mgm. per 100 gms. *Temperature:* 37° to 40.4°C.

Leukocytes: 31,500. *Died* in June. Lead line in x-ray and in microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys.

Case 21. Autopsy No. 14954. A white boy 2 years old chewed the paint from woodwork and toys for three months. Attacks of vomiting appeared five weeks before the present illness and again for about one day before death. For about twenty hours he was drowsy and had episodes of spasticity and flaccidity, slow respirations, choked discs, stiff neck, ankle clonus and hyperactive reflexes. Finally, deep coma and death. *Spinal fluid:* Pandy 3+. Cells 10 per cu.mm. *Blood:* Haemoglobin 63 per cent. Stippled red cells. *Blood lead:* 0.41 mgm. per cent. *Temperature:* 36.2° to 37.4°C. *Leukocytes:* 21,320. *Died* in September. Lead line in x-ray and microscopical sections of ribs. Intranuclear inclusion bodies in liver and kidneys.

Case 22. Autopsy No. 14974. A colored girl, 2½ years old, with history of pica from 9 to 12 months of age. Had projectile vomiting several times the day before death. Became limp and comatose after vomiting, and a little later convulsions appeared, first on the left and then on the right side. Repeated clonic convulsions at half-hour intervals for thirteen hours until death. *Spinal fluid:* Pandy 2+. Cells 5–10 per cu.mm. *Blood pressure:* 105/70. *Pulse:* Irregular. *Respirations:* Irregular and shallow. *Blood:* Haemoglobin 45 per cent. Red blood cells 2,700,000. Stippled red cells. *Temperature:* 38.2° to 39.2°C. *Leukocytes:* 20,940. *Died* in October. Lead line in bones (x-ray and microscopical). Nuclear inclusions in liver and kidneys. Purulent tonsillitis. Few minute tubercles in one lung and confluent tubercles in a bronchial lymph node. Large crusted pustular lesions on extremities like those of impetigo (present for two weeks).

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

PLATE 1. (Hematoxylin and eosin stains)

FIG. 1. Dilated capillaries in the white matter of a cerebral convolution. There is a little serous exudate along the lower margin of vessel at the top in the centre. Case 14. ×100.

FIG. 2. Dilated capillaries in the gray matter of the cerebral cortex. The smooth homogeneous spot within the circle is diffusely filled with serous fluid. Case 12. ×100.

FIG. 3. A mitotic figure in a nucleus in the wall of a capillary in the molecular layer of the cerebellum. Cass 11. ×1170.

FIGS. 4 AND 6. Clumps of swollen nuclei in the walls of capillaries in the molecular layer of the cerebellum. Case 22. ×1170.

FIG. 5. Swollen nuclei in the wall of a capillary in the inferior olive. They project outward, not into the lumen of the capillary. There is a thin irregular film of serous exudate in the tissue outside the vessel. Case 22. ×1170.

FIG. 7. A capillary in the gray matter of the cerebral cortex. The upper horizontal segment is necrotic and occluded. Along the vessel at several points are clusters of minute droplets of exudate in the spongy tissue. Case 16. ×390.

FIG. 8. An arteriole in the gray matter of the cerebral cortex. The wall is necrotic and partly fragmented along the left side. The lumen contains thrombus material. Case 17. ×390.

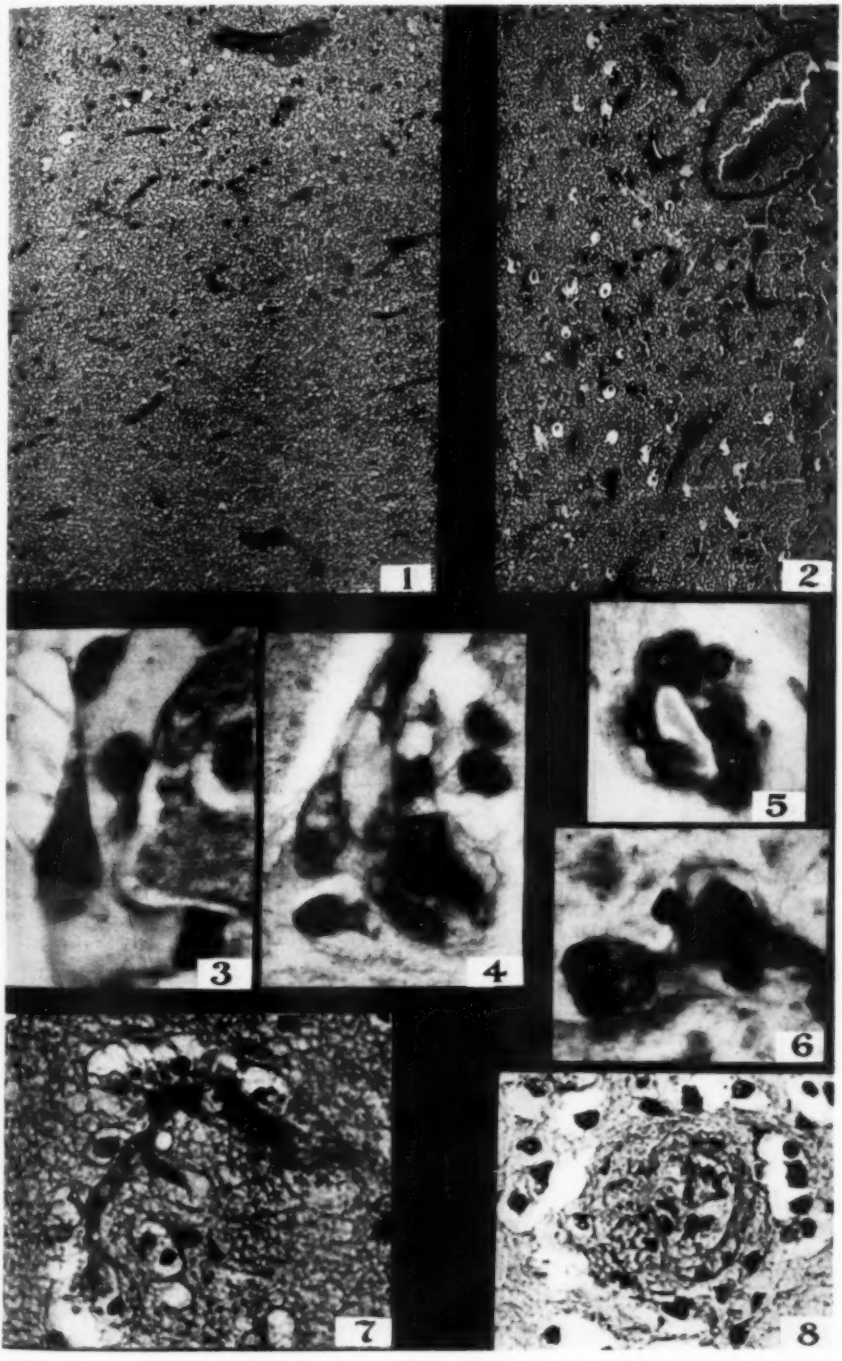

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PLATE 2

FIG. 1. The arrows point to a single drop of serous exudate completely surrounding a segment of a capillary in the molecular layer of the cerebellum. Case 16. H. and E. stain. ×400.

FIG. 2. The arrows point to several drops of exudate coagulated along one margin of a capillary in the gray matter of the cerebral cortex. Case 16. H. and E. stain. ×390.

FIG. 3. A large cluster of drops of exudate about a capillary in the gray matter of the cerebral cortex. Case 12. H. and E. stain. ×390.

FIG. 4. Serous exudate in the meninges of a sulcus between two cerebral convolutions. The exudate is identical in appearance with blood serum in the vessels. Case 19. H. and E. stain. ×100.

FIG. 5. Serous fluid between acini of cells in the anterior lobe of the hypophysis. Case 22. Mann's stain. ×200.

FIG. 6. A large area in the gray matter of the cerebral cortex diffusely infiltrated with serous exudate. The molecular layer at the top is not infiltrated. Case 12. Safranin and light-green stain. ×65.

FIGS. 7 AND 8. Consecutive serial sections stained by different methods to show perivascular serous exudate in the white matter. The section in Fig. 7 is stained with hematoxylin and eosin; in Fig. 8 with safranin and light-green. The sections were mounted at different angles on the slides, but arrows point to the same little vessel in each section, and identical collections of exudate are bracketed with ink. Case 15. ×80.

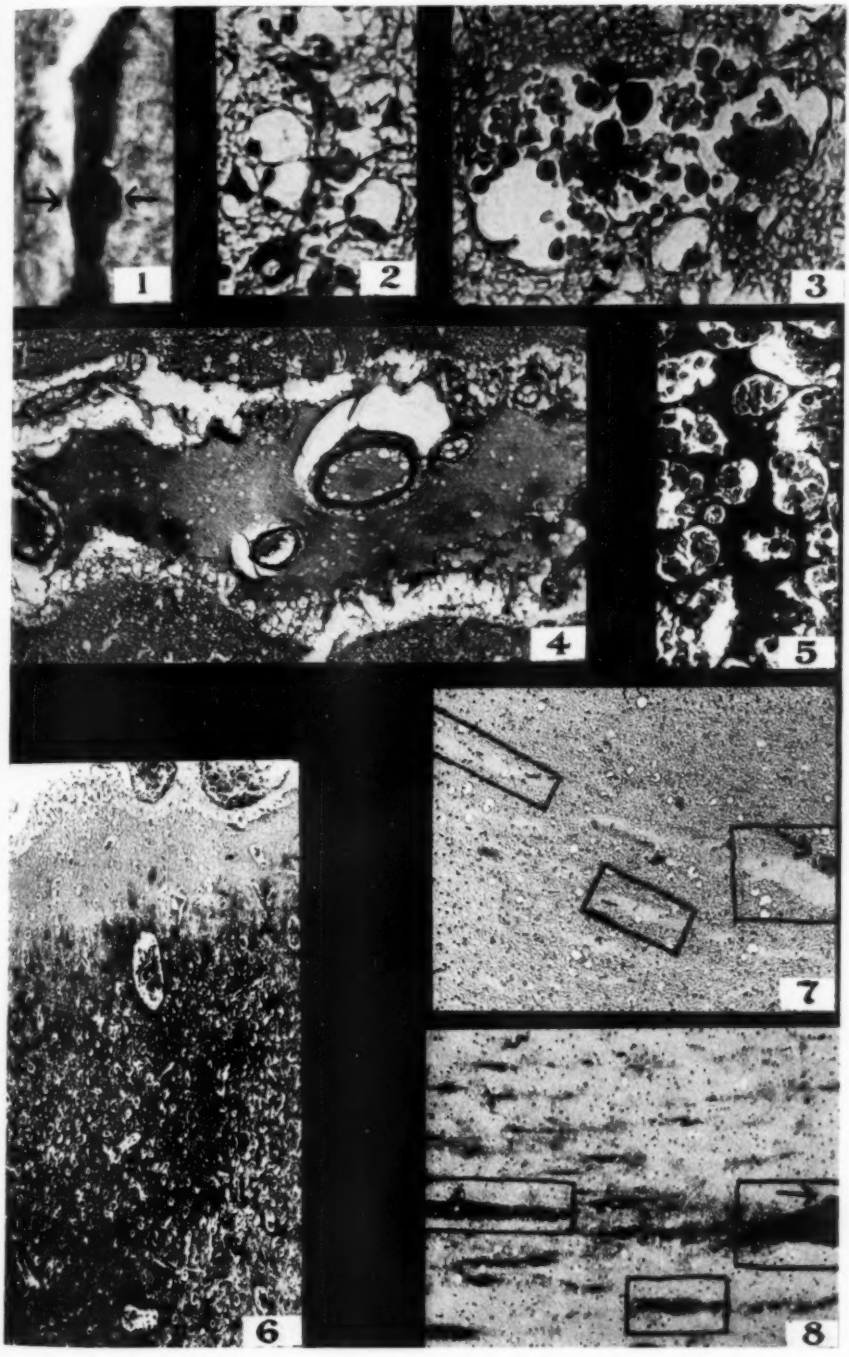

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PLATE 3

FIGS. 1 AND 2. Perivascular and diffuse exudate in the central white matter of a cerebral convolution. In Fig. 1 the section is stained with hematoxylin and eosin. It was decolorized and the exudate shown to better advantage when stained with safranin and light-green (Fig. 2). The arrows point towards a ring of exudate about an arteriole. There is a narrow strip of tissue about the vessel composed of neuroglia and adventitia, torn loose by the exudate. Case 12. ×90

FIG. 3. A low magnification of the whole apical part of the central white matter of one cerebral convolution. The apical white matter is diffusely infiltrated with serous exudate and there is perivascular fluid in gray and white matter. Case 12. Safranin and light-green. ×20.

FIG. 4. Gray matter of the cerebral cortex. In the upper part of the figure extremely porous and vacuolated tissue is shown where most of the nerve cells are necrotic. Case 11. H. and E. stain. ×100.

FIG. 5. Diffuse distortion of the architecture of the gray matter of the cerebral cortex. The fibres are stretched and torn. The parallel arrangement of cells is lost. Case 2. H. and E. stain. ×200.

FIG. 6. Marked disturbance of architecture in a narrow zone at the junction of gray and white matter. Case 16. H. and E. stain. ×100.

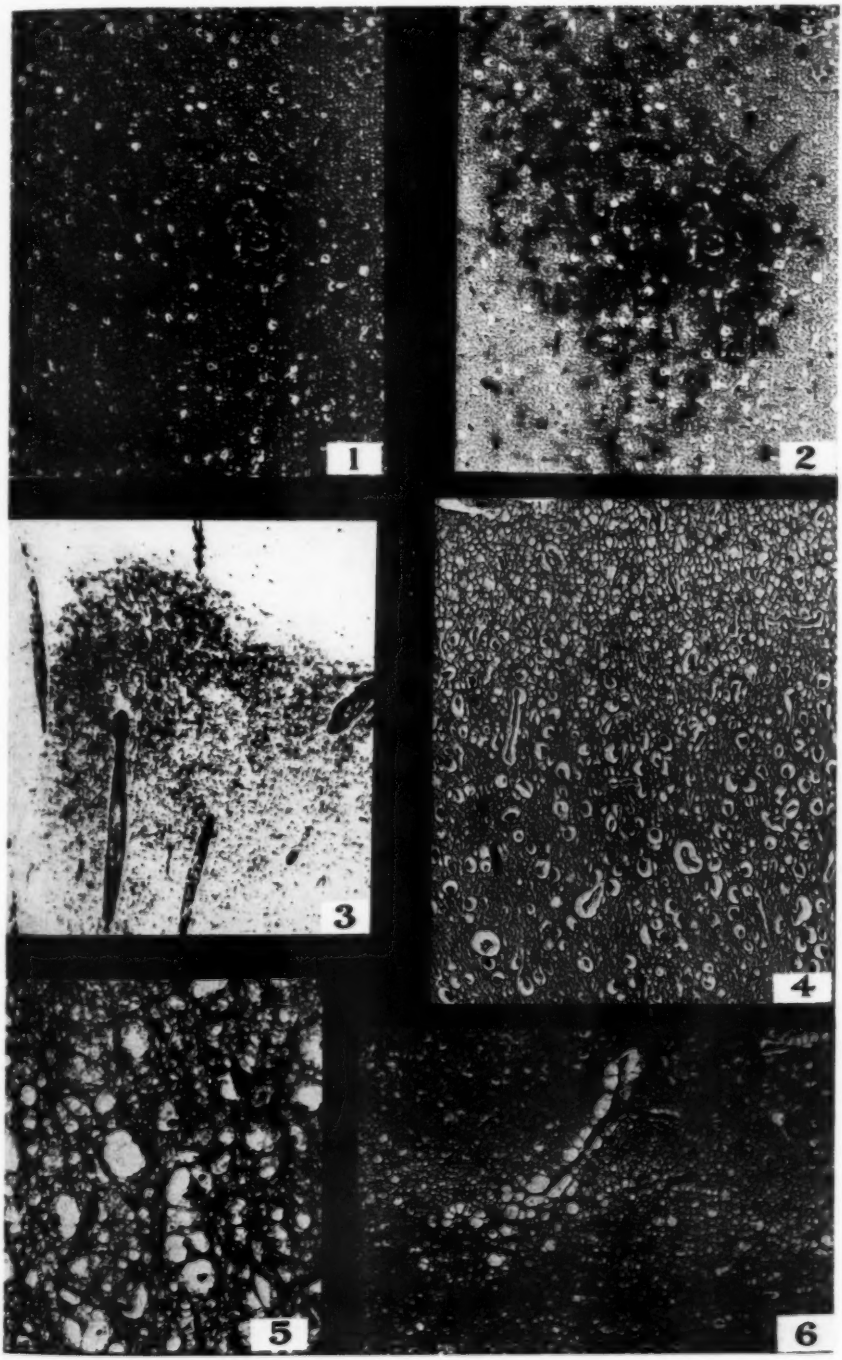
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Plate 4

Fig. 1. The meninges and molecular layer of the cerebral cortex. A narrow superficial zone of tissue is extremely spongy. Fibres are stretched and torn. The inner layer of the pia mater is torn loose and pushed upward. There is some perivascular serous exudate which is continuous with a number of little streams of fluid in the spongy molecular layer. Case 14. H. and E. stain. ×100.

Fig. 2. A torn distorted superficial zone in the molecular layer of the cerebral cortex. The pia mater is displaced. In the centre small confluent collections of serous fluid and several pyknotic glial nuclei are shown. Case 16. H. and E. stain. ×200.

Fig. 3. A group of large astrocytes with swollen nuclei in the molecular layer of the cerebral cortex. Case 11. H. and E. stain. ×200.

Fig. 4. Fat-laden glial cells in the molecular layer of the cerebral cortex. Case 11. Osmic acid stain. ×200.

Fig. 5. Low magnification of the central white matter of a cerebral convolution. There are numerous localized foci of extremely porous torn tissue. Case 19. H. and E. stain. ×35.

Fig. 6. Higher magnification of similar torn tissue about a capillary in the gray matter of the cerebral cortex. Case 19. H. and E. stain. ×200.

Fig. 7. A localized area of torn spongy tissue still partly filled with serous exudate. Case 19. H. and E. stain. ×200.

Figs. 8 and 10. A pool of exudate (Fig. 8) has torn through the white matter leaving a narrow strip of damaged fat-laden glial cells attached to the adventitia of the arteriole. Single cells and clumps of cells lie free in the fluid. Case 14. H. and E. stain. In Fig 10 (Case 14) the fat-holding cells are shown stained with osmic acid. ×200.

Fig. 9. Low magnification of central white matter of a cerebral convolution. There is loss of tissue in wide zones about blood vessels. The fibres that remain in the spongy areas are necrotic and fragmented. Case 14. Weil's stain for myelin sheaths. ×80.

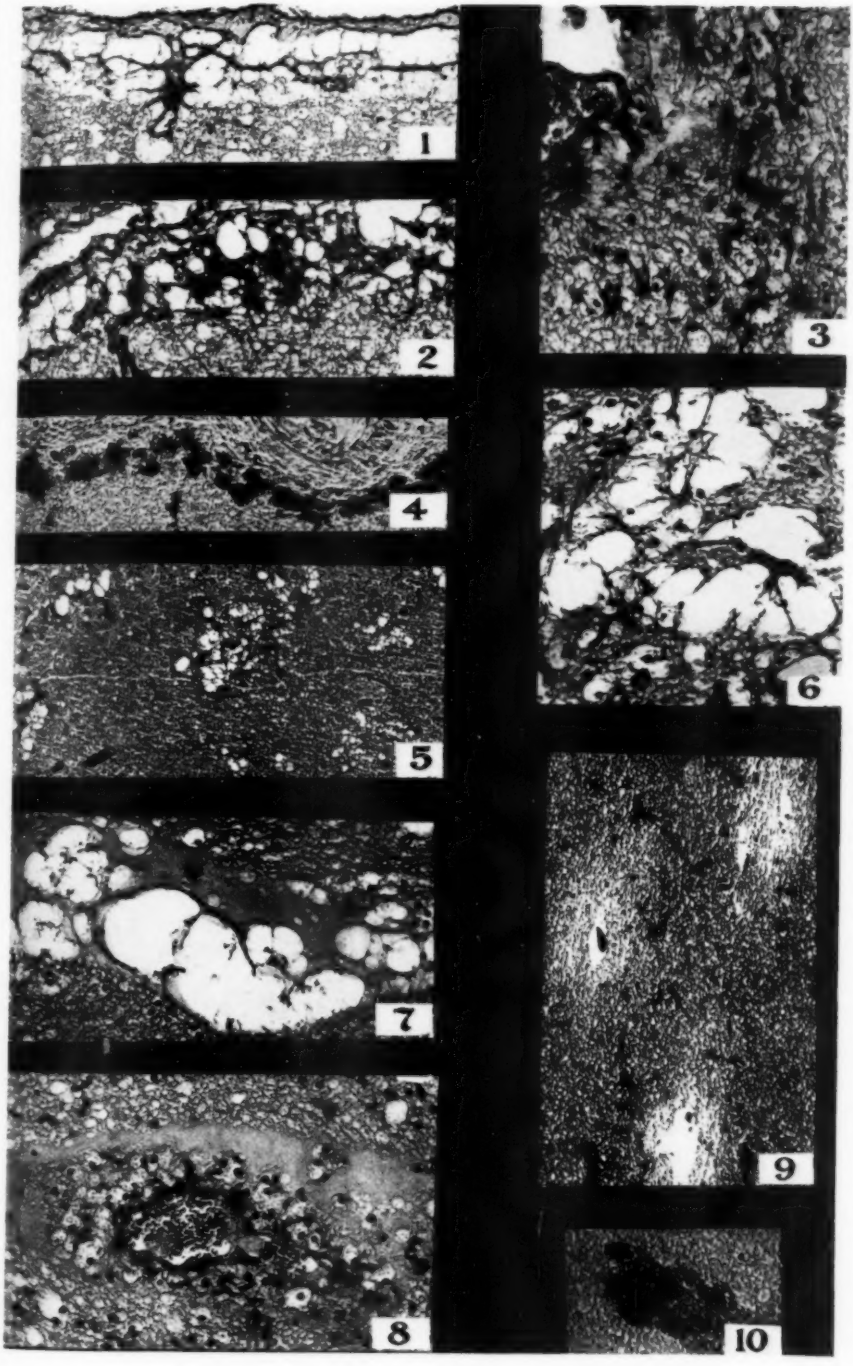

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PLATE 5. (Hematoxylin and eosin stains)

FIG. 1. A small focus of necrotic tissue and peripheral haemorrhage in the motor nucleus of the 5th cranial nerve. Case 18. ×200.

FIG. 2. An area of necrosis with peripheral growth of glial cells in the white matter of the insula. The arrow points to a mitotic figure. Case 4. ×390.

FIG. 3. Two necrotic nerve cells in the thalamus. There are four or five neurophagocytes about the upper nerve cell and more numerous ones about the lower cell. Case 10. ×390.

FIG. 4. A small focus of necrosis, and glial cells in the peripheral spongy tissue in the cerebral cortex. Case 20. ×200.

FIG. 5. A fresh area of necrosis and peripheral haemorrhage in the cerebral white matter. Case 20. ×200.

FIG. 6. A rosette of neuroglia about a centrally placed necrotic nerve cell in one of the geniculate bodies. Case 2. ×390.

FIG. 7. Distorted architecture and numerous large astrocytes in the apical white matter of a cerebral convolution. Case 11. ×200.

FIG. 8. A rosette of glial cells about a necrotic nerve cell in the thalamus. Case 14. ×390.

FIG. 9. A single necrotic nerve cell in the cerebral cortex without appreciable glial reaction. Case 20. ×390.

FIG. 10. A nodular collection of neuroglia in a focus of necrotic tissue in the gray matter of the cerebral cortex. Case 17. ×200.

FIG. 11. A small focus of necrotic tissue and peripheral gliosis in the white matter of the spinal cord. Case 2. ×390.

FIG. 12. Focus of necrotic tissue and peripheral glial cells in the brachium conjunctivum. Case 18. ×390.

FIG. 13. The arrow points to the nucleus of a necrotic nerve cell accompanied by neurophagocytes in one anterior horn of the lumbar spinal cord. Case 14. ×390.

FIG. 14. On the right a normal nerve cell in the thalamus is shown. On the left is the remnant of a necrotic nerve cell surrounded by a few glial cells. Case 10. ×390.

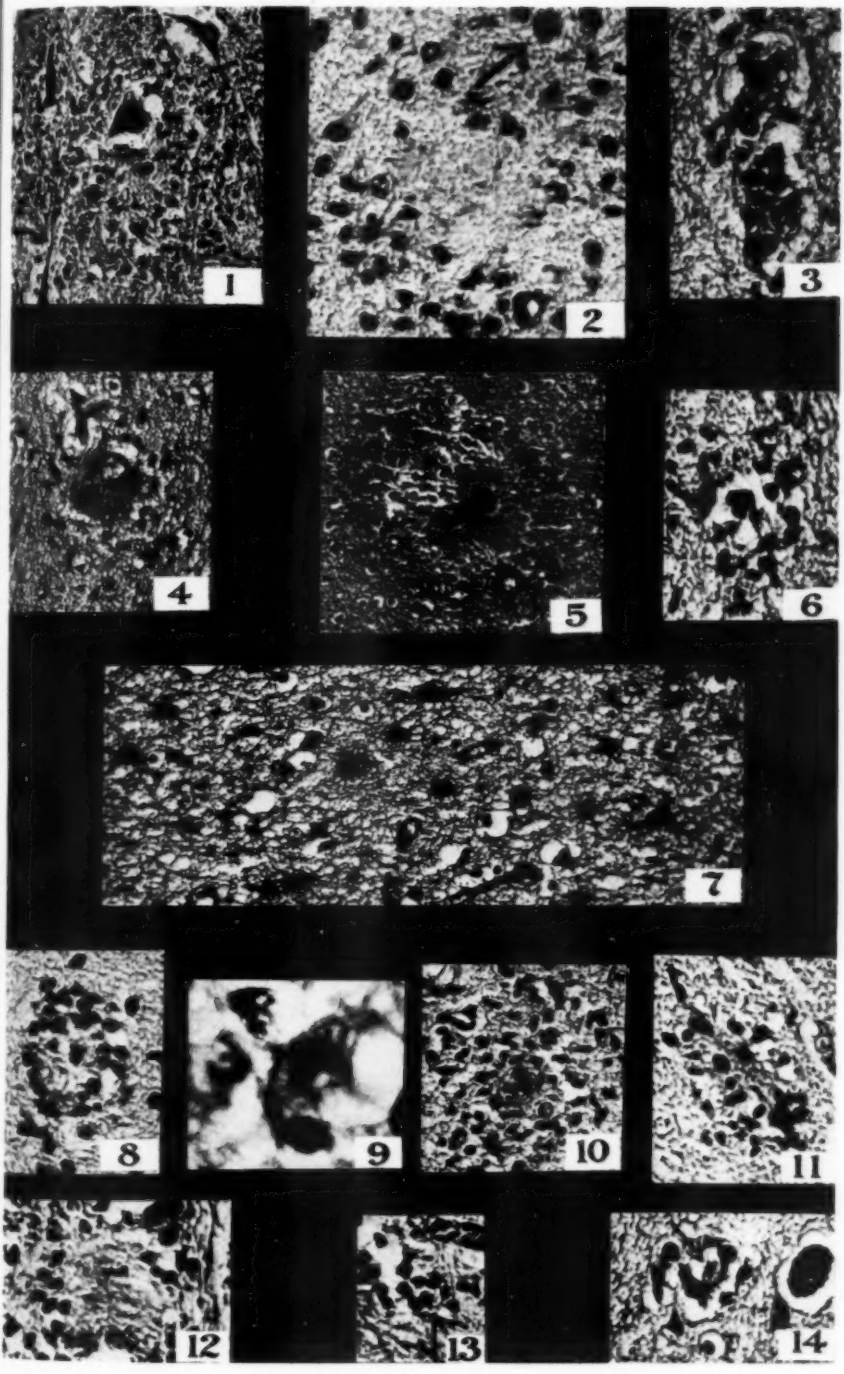

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PLATE 6. (Hematoxylin and eosin stains)

FIG. 1. Perivascular serous exudate in the white matter of the cerebellum. Case 14. ×50.

FIG. 2. Serous exudate and torn necrotic tissue in the Purkinje layer of the cerebellum. Case 19. ×200.

FIG. 3. Extensive necrosis and loss of tissue in the white matter of the cerebellum. Case 14. ×50.

FIG. 4. The arrows point to necrotic Purkinje cells. The rest of the Purkinje layer is stretched and torn and devoid of nerve cells. Case 15. ×200.

FIG. 5. Distorted architecture and new glial cells in spongy patches of the molecular layer of the cerebellum. Case 17. ×200.

FIG. 6. Necrotic glial cells scattered in the white matter of the cerebellum. Case 14. ×390.

FIG. 7. A thrombus in a necrotic capillary segment in the cerebral cortex. Within the circle are minute and larger droplets of inspissated exudate. Case 16. ×390.

FIG. 8. Shows (1) a narrow superficial zone of torn spongy tissue in the molecular layer of the cerebellum, (2) small round cells of the marginal embryonic stratum and the inner layer of pia mater torn from the surface and forced outward, (3) serous exudate in the subarachnoid space at the top of the figure. Case 14. ×200.

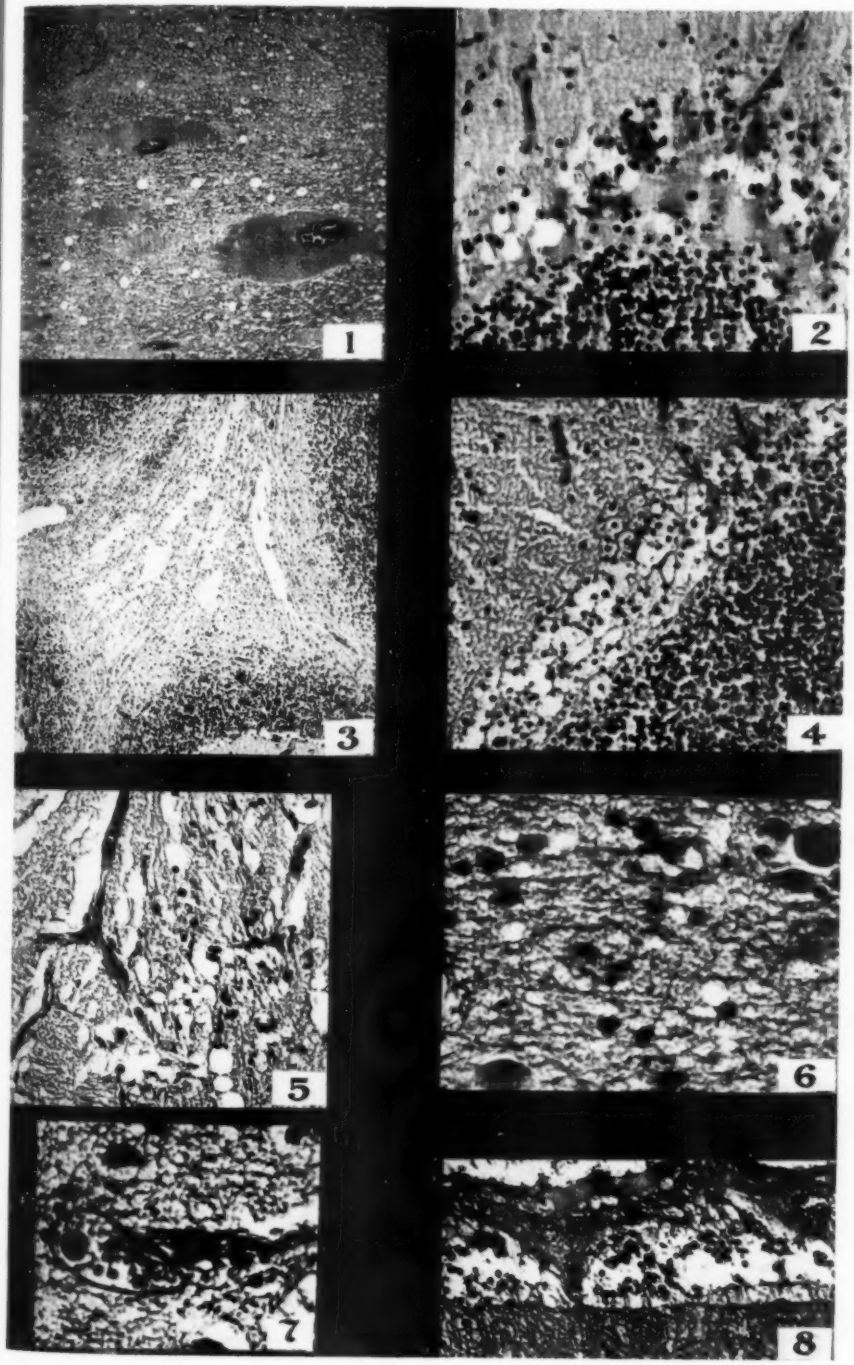

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PLATE 7

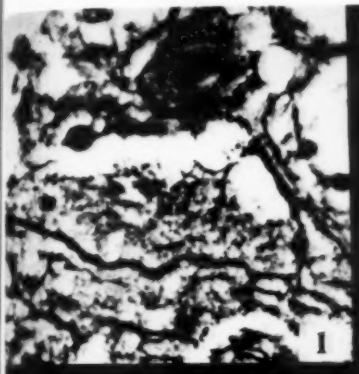
FIGS. 1 AND 2. Cerebellum, Case 14. Bodian's silver stain for axis cylinders. Figure 1 shows a normal Purkinje cell and fibres of basket cells which run horizontally in the molecular layer and end around the Purkinje cells. In Fig. 2 is shown an area from which the Purkinje cells and the dendrites of basket cells have disappeared. ×670.

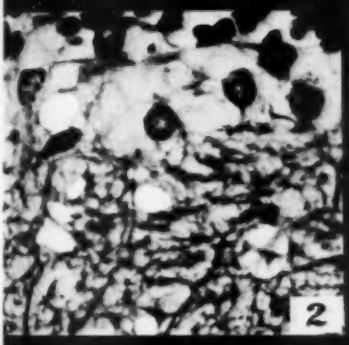
FIGS. 3 AND 4. Dentate nucleus of cerebellum, Case 2. H. and E. stain. Fig. 3 shows loss of many nerve cells and diffuse new growths of neuroglia. In Fig. 4 a more normal area in the same dentate nucleus is shown for comparison. ×200.

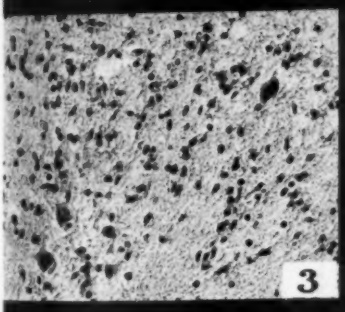
FIG. 5. Extensive destruction of tissue in the molecular layer of three folia of the cerebellum. Most of the remaining tissue is composed of neuroglia. The arrows point to collections of basophilic material resembling calcium. The adjacent meninges are somewhat scarred and are infiltrated with lymphocytes. Case 19. H. and E. stain. ×100.

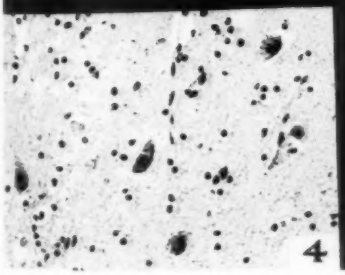
FIG. 6. Diffuse atrophy, loss of cells and fibres, and gliosis affecting several folia of the cerebellum. More normal folia are shown below at the right. Case 18. H. and E. stain. ×25.

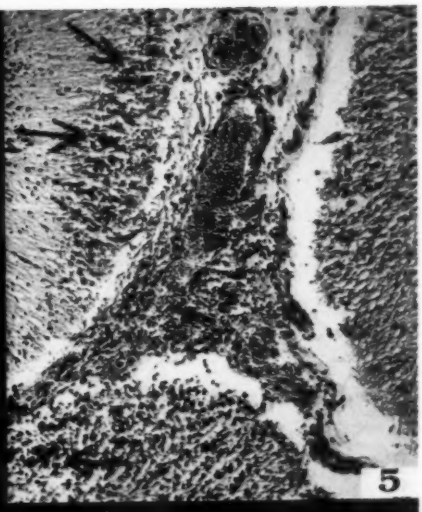
FIG. 7. Irregular growth of neuroglia in patches in the molecular layer of the cerebellum. Only a single Purkinje cell remains. Lymphocytes about a blood vessel in the meninges. Case 19. H. and E. stain. ×100.

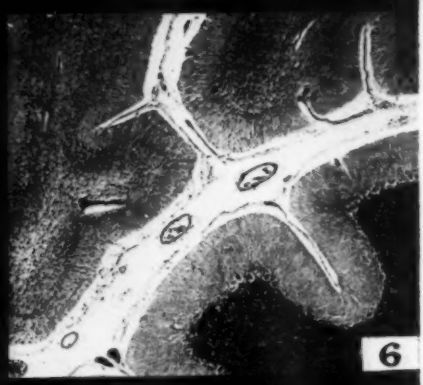












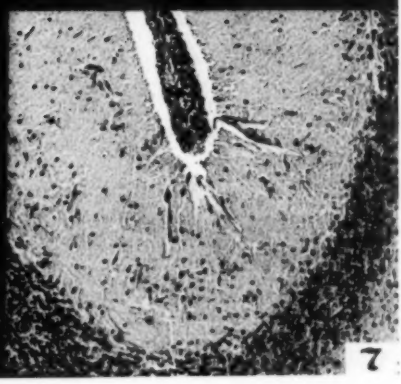


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PLATE 8. Case 18. (Hematoxylin and eosin stains)

FIGS. 1, 2, 3, AND 4. Old basophilic exudate resembling calcium about capillaries and arterioles in the cerebral cortex (Figs. 1 and 4; ×100), and molecular layer of the cerebellum (Figs. 2 (×200), and 3; (×1170)). Fig. 3 shows many tiny drops adherent to the wall of a capillary (oil immersion, ×1170).

FIG. 5. Basophilic plaques in the wall of an artery in the putamen. ×100.

FIG. 6. A group of pigmented and non-pigmented cells about an artery in the white matter of the pons. ×390.

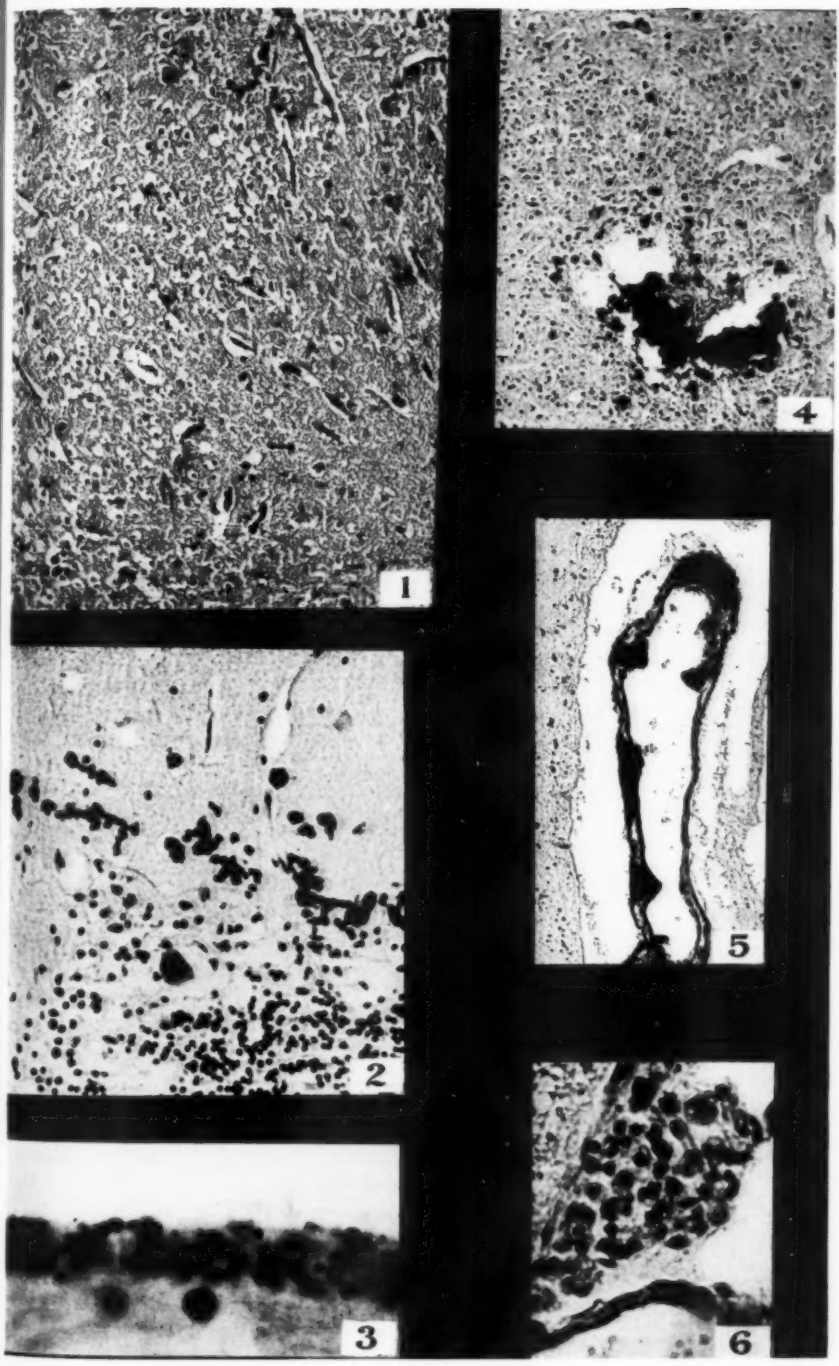

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PLATE 9

FIG. 1. A fresh area of necrosis in the inferior olive with a central capillary thrombus and peripheral ring of haemorrhage. Case 20. H. and E. stain. ×390.

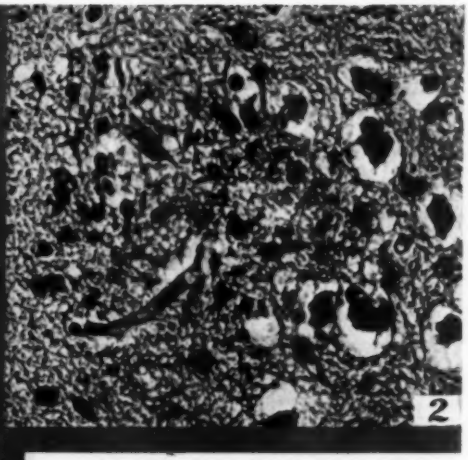
FIG. 2. A larger nodule in the inferior olive composed of neuroglia which has replaced the normal tissue. Nerve cells may be seen at the right. None are left in the glial nodule. Case 17. H. and E. stain. ×390.

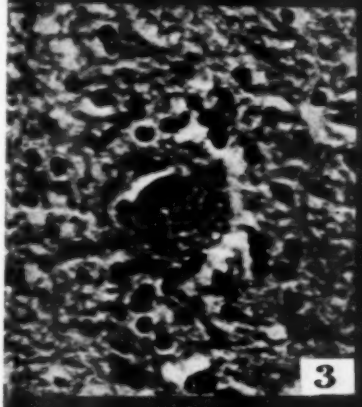
FIG. 3. A thrombus in an arteriole. Glial reaction in the tissue immediately about the vessel. Case 18. H. and E. stain. ×390.

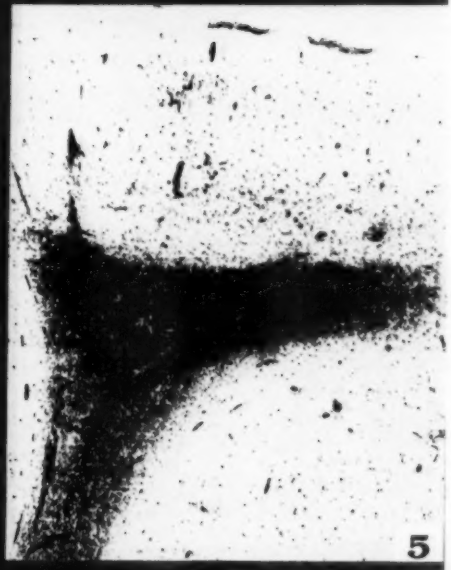
FIG. 4. Capillary thrombus and focus of necrotic tissue without haemorrhage in the cerebral white matter. Case 20. H. and E. stain. ×390.

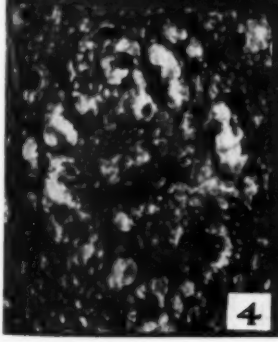
FIG. 5. A cerebral convolution in which the central white matter is diffusely saturated with serous exudate. Perivascular fluid may be seen in the gray matter. Case 12. Safranin and light-green stain. ×12.

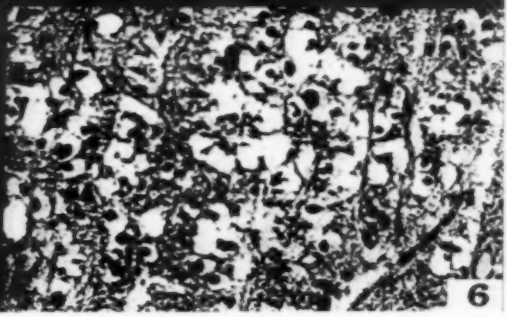
FIG. 6. Cerebral cortex of a child dying a year and a half after onset of the original symptoms. There is extensive patchy destruction and loss of tissue. Case 7. H. and E. stain. ×200.











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THE PRODUCTION OF HYALINE ARTERIOLOSCLEROSIS AND ARTERIOLONECROSIS BY MEANS OF PROTEOLYTIC ENZYMES

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In a recent study of the pathogenesis of acute haemorrhagic pancreatitis the writers showed that the haemorrhage in that condition results from a peculiar type of necrosis of the walls of blood vessels in the substance of the gland, and that this vascular lesion is caused by the necrotizing action of escaped pancreatic secretion (1). The agent in the secretion responsible for the dissolution of the vessel walls was shown to be the proteolytic ferment. It was found that juice taken directly from the duct, without contact with enterokinase, has the power to produce vascular necrosis, and the mechanism of activation of trypsinogen when it escapes into the tissues was discussed in the above mentioned paper. It was furthermore shown that not only pancreatic duct juice, but also commercial and purified crystalline (Northrop) trypsin produce at any site of injection precisely the same type of vascular necrosis and rupture as that which we regularly found in the pancreas in haemorrhagic pancreatitis.

During the course of the above mentioned studies we were interested to find frequently in the pancreas, in both human and experimental haemorrhagic pancreatitis, arterioles which had the histological characteristics familiar in the hyaline arteriolosclerosis that is so often associated with hypertension and nephritis in the human being; and in our experiments in which pancreatic juice or trypsin was injected into the subcutaneous tissues of dogs an identical vascular lesion was regularly found by the side of the vessels with more complete destruction and rupture of their walls. Since there is so little information at present regarding the etiology and mode of development of hyaline arteriolosclerosis in the human being we have felt that any discovered

means of reproducing this specific type of lesion experimentally should be recorded.

EXPERIMENTAL PROCEDURES

Pancreatic Duct Juice of Dogs. Dogs were starved for 36 to 48 hours, and then fed a large meal of meat and milk 2 to 3 hours before the operation. Under aseptic precautions the abdomen was opened in the mid-line and the duodenum gently drawn up into the wound. The accessory pancreatic duct was exposed by gently separating the adherent lobules of the pancreas from the duodenum in the region of the duct. A ligature was placed about the duct and tied tightly near the duodenum. The duct was then opened and a glass cannula, inserted toward the pancreas, was tied in place. The dogs were kept under light ether anaesthesia during the collection of the juice. When 1 or 2 cc. of secretion had accumulated in a sterile container, it was taken up in a sterile syringe and used for injection into the subcutaneous tissues of another dog. Part of the juice collected was cultured, and in each case proved to be sterile.

Commercial Pancreatic Trypsin. This trypsin was made from beef pancreas and, according to the statement of the manufacturers (Fairchild Bros. and Foster, New York City), was free from lipase and diastase, and contained no preservative or other added substance. One gram of the powder was added to 20 cc. of normal saline, the mixture shaken for 15 minutes and then centrifugalized. The supernatant fluid was pipetted off from the insoluble sediment and passed through a Berkefeld filter for immediate use. The solution, sterile on culture, dissolved fibrin rapidly at 37°.

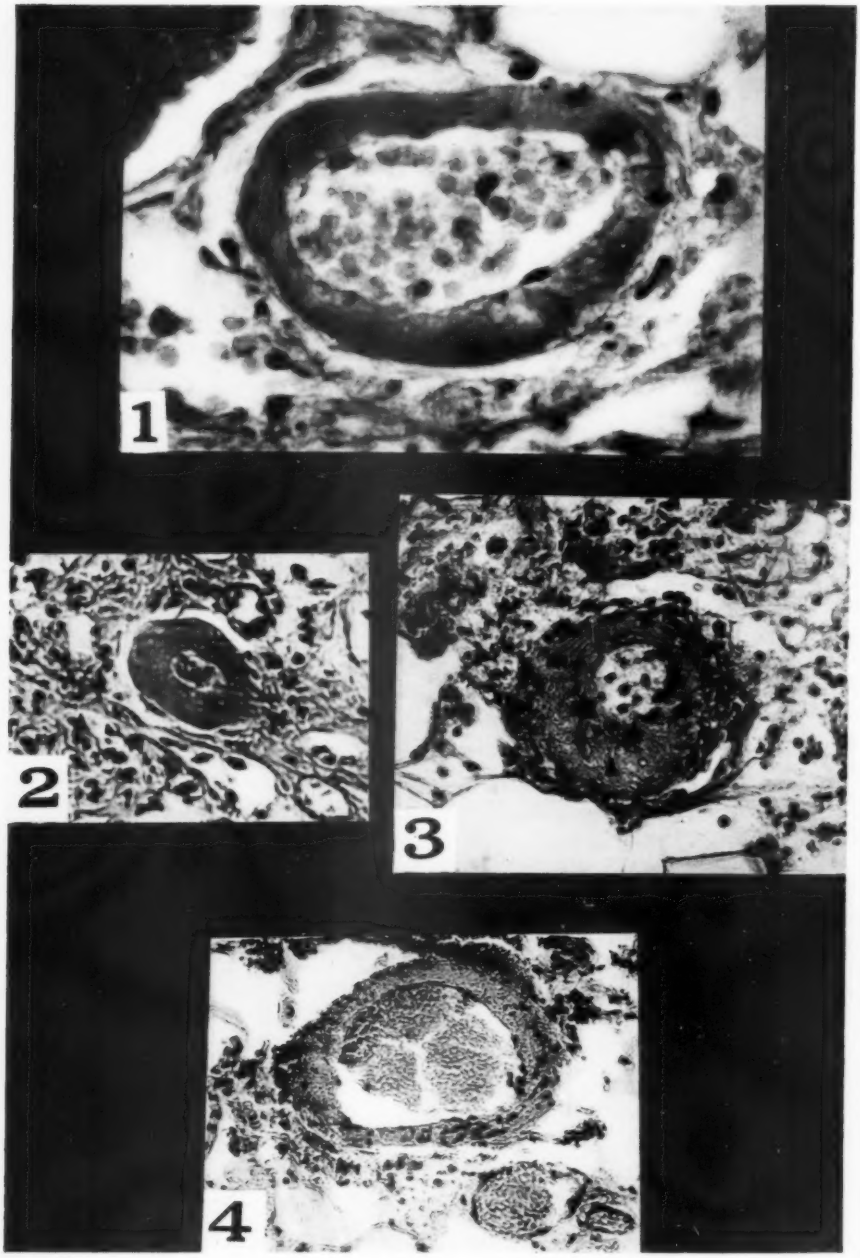
Purified Crystalline Pancreatic Trypsin. Through the kindness of Dr. J. H. Northrop, of the Rockefeller Institute at Princeton, N. J., we obtained samples of crystalline pancreatic trypsin and crystalline pancreatic chymo-trypsin, the preparation and properties of which have been described by Northrop and Kunitz (2). Solutions of these preparations were made, according to instructions, by dissolving each in 100 times its weight of N/200 HCl. The solutions were passed through a Berkefeld filter and proved to be sterile by culture. Since the dry samples of the enzymes contained 50 per cent of magnesium sulphate, control injections of 0.5 gram of magnesium sulphate in 100 cc. of N/200 hydrochloric acid were made. No vascular lesions resulted.

Trypsin of Plant Origin. Papain is a well-known trypsin-like enzyme (3) obtained from the fruit of the paw-paw tree (Carica papaya). Solutions of papain (Merck) were prepared by adding 1 or 2 grams of the powder to 20 cc. of normal saline. The mixture was shaken for 15 minutes and centrifugalized, the supernatant fluid was pipetted off from the insoluble residue, passed through a Berkefeld filter, and its sterility proved by culture.

Three-tenths to one cubic centimeter of each of the sterile solutions obtained in the above manner was injected at different sites into the

subcutaneous tissue of normal dogs. The sites of injection were marked with ink and twenty-four hours later they were excised, fixed in Zenker-formol and sectioned for histological study.

In addition to the more corrosive effects leading to vascular rupture and haemorrhage, as described in our former paper, each of the above-mentioned solutions (pancreatic duct juice, commercial trypsin, crystalline trypsin, crystalline chymotrypsin, papain) produced arteriolar lesions which in all respects had the histological appearance characteristic of human hyaline arteriolosclerosis (Figs. 1, 2, 3). The cellular structure of the media of these arterioles disappeared completely, leaving only a homogeneous hyaline substance which was sometimes faintly basophilic, as is not infrequently the case in human hyaline arteriolosclerosis, and sometimes purely eosinophilic. In some vessels only a segment, in others the entire circumference was affected. Fat stains have revealed no lipoid in the affected vessels. There are, of course, many hyaline arterioles in human arteriolosclerosis that contain no demonstrable fat, and it is generally believed that fat is absent in the fresher human lesions. Whether lipoid would eventually be deposited in the vessels damaged by trypsin we cannot say at present. In some cases the wall of the vessel was so thickened by the hyalinizing process that the lumen was narrowed (Fig. 2). In some partially and less intensely affected vessels the earliest change consisted in the appearance of a hyaline material, suggesting fluid, beneath the endothelium and between muscle fibers. In other arterioles necrosis of the media was obvious. The muscle fibers had lost their outlines and identity, their cytoplasm being converted into a formless, granular, pink-staining material, and fragments of nuclei could still be seen in their walls. These vessels (Fig. 4) had precisely the appearance of the "smudgy," freshly necrotic arterioles familiar in the more fulminant cases of arteriolosclerosis in the human being (the so-called "necrotizing arteriolosclerosis" or "arteriolonecrosis"). In no case have we encountered vascular lesions of either the hyaline or necrotic type in untreated dogs, in untreated areas of the experimental animals, or in areas into which samples of the enzyme solutions prepared in the same manner but inactivated by heating for 10 minutes in a bath of boiling water were injected. The solution of magnesium sulphate used as a control for the crystalline trypsin, for the reason mentioned



FIGS. 1–4

above, was highly irritating and produced massive local oedema and inflammation, but no lesions of arteries or arterioles. Injections of sterile bile caused local oedema, inflammation and also necrosis of tissue, but no vascular lesions of the type here described. It may be stated that the action of the ferments appears to be more pronounced upon the walls of blood vessels than upon adjacent epithelial structures (hair follicles, breast tissue).

There are two points relating to the development of these lesions that merit especial comment. In the first place, we were rather surprised to find that the process of hyalinization of the necrotic media could occur with such rapidity. Within 24 hours after injecting the proteolytic enzymes the walls of some of the arterioles at the sites had not only undergone complete necrosis but had lost all nuclear and cytoplasmic structure and had become uniformly hyalinized. The rapidity with which death and hyalinization of the media can occur may, perhaps, permit us to understand the curious fact that so often in human arteriolosclerosis practically all of the affected arterioles show only completed hyalinization and none of the usual evidences of fresh necrosis (*e.g.*, nuclear fragments, granular necrotic cytoplasm), and this even in cases in which we have reason to believe that the necrotizing process is actively progressive. Certainly, the present

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Explanation of Illustrations

(Photographs by Mr. Milton Kougl)

FIG. 1. HYALINE ARTERIOLE AT SITE OF INJECTION OF COMMERCIAL TRYPSIN SOLUTION, 24 HOURS AFTER INJECTION

The cellular structure of the media has entirely disappeared

FIG. 2. HYALINE ARTERIOLE IN SUBCUTANEOUS TISSUE AT SITE OF INJECTION OF PANCREATIC DUCT JUICE, 24 HOURS AFTER INJECTION

The cellular structure of the media has entirely disappeared, and the vessel wall is greatly thickened.

FIG. 3. HYALINE ARTERIOLE IN SUBCUTANEOUS TISSUE AT SITE OF INJECTION OF THE PLANT TRYPTIC FERMENT, PAPAIN, 24 HOURS AFTER INJECTION

Most of the structure of the media has disappeared, but a few muscle fibres remain intact. The hyalinized segment at the bottom is greatly thickened.

FIG. 4. NECROTIC ARTERIOLE AT SITE OF INJECTION OF CRYSTALLINE TRYPSIN (NORTHROP) INTO SUBCUTANEOUS TISSUE, 24 HOURS AFTER INJECTION

The muscle fibers of the media are necrotic. Nuclear fragments are present in the granular, necrotic wall.

observations make it clear that a completely hyalinized arteriole does not necessarily imply a chronically diseased arteriole. The vessel may have been perfectly normal several hours before.

Another point deserving comment is the rapidity with which the wall of the affected vessel may be greatly thickened by the hyalinizing process (Figs. 2, 3). This rapid thickening of the necrotic wall must result from imbibition. It has frequently been suggested that the thickened, hyalinized arterioles in human arteriolosclerosis may be the result of hypertension causing marked hypertrophy of the muscular coat of the vessel or "hyperplastic sclerosis" of the intima, with subsequent death of the cells from "overstrain," followed by hyalinization of the dead cells. While there is little doubt that hypertension can produce hypertrophy of the medial muscle fibers, it has been rather difficult for many to believe that medial necrosis and hyalinization result simply from overwork. In the first place, exactly similar changes are frequently found here and there in the body in the absence of hypertension. In the spleen, for example, marked hyaline arteriolosclerosis is so common that it would be a rash person who would suggest from the finding of arteriolosclerosis in that organ that the patient had had hypertension during life. On the other hand, cases of chronic nephritis with hypertension may show no appreciable hyaline arteriosclerosis. Finally, it is rather difficult to regard the more fulminant cases of arteriolosclerosis with widespread fresh necrosis and haemorrhage (arteriolonecrosis) as being due simply to the strain that hypertension places upon the vessels. The lesions suggest more strongly the effects of some injurious, toxic agent. That injurious agents have the power to produce this type of lesion in the human being is clear from the fact that vessels attacked by the unknown agent responsible for periarteritis nodosa often exhibit the typical changes of hyaline arteriolosclerosis in the segment involved in the inflammatory process, and this in cases with no hypertension whatever. It is, however, probable that there is no single cause of arteriolosclerosis, and perhaps hypertension alone may be able to produce these extraordinary effects. We may hope for light on this specific point from experiments on the artificial production of hypertension, such as those at present being carried out so carefully by Goldblatt (4). The present experiments demonstrate only that

thickening of the vessel wall and hyalinization, and also all features of arteriolonecrosis, can rapidly occur in vessels which only a few hours before were perfectly normal. Neither hypertension, hypertrophy of the media nor "hyperplastic sclerosis" of the intima are necessary precursors of thickening of the wall and narrowing of the lumen of the vessel.

The exact mechanism by means of which these proteolytic ferments cause destruction of the vessel walls cannot at present be stated with any assurance. Whether the proteolytic ferment acts directly upon the vessel, or whether some product of protein digestion is responsible we are unable to say. It is interesting, however, to note that following our preliminary report of the production of this vascular lesion by proteolytic ferments (5), Mellon, Baker and McIlroy (6) have succeeded in producing a similar lesion by the injection of the protein decomposition product allylamine.

In reporting here the fact that proteolytic enzymes of plant and animal origin have the power of producing arteriolar lesions resembling in all essential respects the lesions of human hyaline arteriolosclerosis and arteriolonecrosis, it is far from our intent to imply that the lesions of this type in the human being must therefore be caused by proteolytic ferments. While it is believed by some that bacterial infection may be causally related to human arteriolosclerosis, and while plant trypsin (papain) was highly active in causing arterial lesions in our experiments, it would be altogether unwarranted, of course, to conclude from our present information that bacterial enzymes, or other proteolytic ferments, play a primary rôle in the etiology of human arteriolosclerosis. The local concentration of the ferments in our experiments was high; the relative ability of bacterial proteolytic ferments to cause the lesion is at present being investigated; the effect of the products of proteolytic digestion requires study; and nothing is known of the level of antitrypsin (ferment neutralizing power) of the blood in cases of human arteriolosclerosis. We have presented our observations simply for the purpose of recording the fact that, under the conditions of our experiments, proteolytic enzymes have the power to cause localized arteriolar lesions characteristic of arteriolosclerosis, and to point out the rapidity with which arteriolar changes which have often been regarded as requiring a considerable length of time for their development may occur.

CONCLUSIONS

Arteriolar lesions having the characteristics of human hyaline arteriolosclerosis and arteriolonecrosis occur at the site of injection of tryptic enzymes of animal or plant origin (pancreatic juice, commercial or crystalline trypsin, papain).

Complete necrosis and hyalinization of the vessel walls can occur within 24 hours.

Neither previous medial hypertrophy nor intimal proliferation is essential for the thickening of the affected vessel wall with consequent narrowing of the lumen. These changes can take place, apparently by imbibition, within 24 hours.

Whether the proteolytic enzymes act directly upon the vessel wall, or whether the lesion results from the action of products of protein decomposition, is at present undetermined.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Allergic Diseases—Their Diagnosis and Treatment. By RAY M. BALYEAT, M.A., M.D., F.A.C.P., assisted by RALPH BOWEN, B.A., M.D., F.A.A.P. Fourth edition, revised and enlarged. 516 pp. $6.00. (*F. A. Davis Co., Philadelphia, 1936.*)

Text-books on allergic disease are becoming increasingly common; much more, apparently, than fundamental advances in this field would justify.

The large clinical material afforded in Dr. Balyeat's clinic should be of great value in the compilation of a text but unfortunately the data throughout this book suffer from empiric and uncritical treatment. The chapters devoted to the geographical distribution and botanical characteristics of the various pollens are excellent; Dr. Balyeat is recognized as a well informed botanist. Much space is devoted to the comparatively new method of treatment of chronic asthma by the injection of iodized oil into the bronchial tree; but the analysis of the results obtained by this method is too limited to allow definite conclusions concerning its value. Again the chapters on eczema, urticaria and contact dermatitis are disappointingly elementary. Further, that such illnesses as migraine and Menière's Disease are due to an allergic mechanism is seriously questioned by any physician not an allergist, and even by some allergists, and the lack of critical discussion of the rôle which allergy may play in these diseases is too apparent.

W. L. W.

Ultra-sons et Biologie. By A. DOGNON, E. and H. BIANCANI. 80 pp. Illus. Unbound. 25 fr. (*Gauthier-Villars, Paris, 1937.*)

Introduced by 'Ultra-sons et Biologie,' and dedicated to the elucidation of the known facts regarding the effects of radiations on living organisms, the new series "Collection des Actualités Radiobiologiques" promises to organize the new field of radiation biology into a readily accessible branch of science.

The reader inexperienced in super-sonics, finds in this short volume sufficient development of the underlying physical characteristics of these short sound waves and their production to grasp their importance and applicability to medical and biological problems. General characteristics, such as wave-length, frequency, velocity and its dependence on compressibility and density, and the idea of stationary waves, of compressional waves in elastic media are briefly discussed to orient the reader. Aspects peculiar to the utilization of the quartz piezo-electric vibrator are discussed, in which are brought out the dependence of intensity on voltage and frequency along with their practical limitations. Such physical phenomena as

pressure gradients and cavitation which play important rôles in the physical as well as biological effects of super-sonics are presented in an interesting manner. Also reflection and absorption of the waves in different media occupy the attention of the reader in a deserving presentation.

In order to correlate biological phenomena which follows, in an attempt to arrive at the mechanism by which this new source of mechanical energy alters the living cell, brief mention is made of some of the most interesting chemical and physical-chemical effects of supersonics which have been observed and reported. Of particular interest are: liberation of iodine, activation of oxygen, dispersion and flocculation of solids and liquids in various media.

Extremely interesting are the many and diverse biological effects described which include protoplasmic rearrangements and recovery in cells, probable physiological reactions of cells and organisms, cellular explosions, resistance of bacteria to ultra-sonic lethal actions, and the destruction of some multi-celled organisms.

Nearly all of the fascinating effects described by the authors are very dependent upon external conditions such as external pressure, concentration of suspensions and the dispersing medium employed, which indicates the need of future work to be carried out in this new and interesting field of energy transformations.

Perhaps the most important of the contributions of the authors is the preliminary analysis of a mechanism which very likely controls many of the most startling of the biological actions produced by ultra-sonic vibrations in a liquid medium. High pressure gradient of the cavitation wave is given great emphasis in the following—"The origin of the cavitation bubble is a veritable explosive phenomenon, which is the point of departure of a compression wave of considerable amplitude. It is this wave of compression which is responsible for the cellular bursting."

The monograph is completed with possible projections of biological and medical applications of these high frequency compressional waves as well as the possibility of using such waves by living organisms for some sort of communication. A selected bibliography of sources adds value to this little volume.

R. S. A.

Surgical Pathology of the Thyroid Gland. By ARTHUR E. HERTZLER. 298 pp. Illus. $5.00. (*J. B. Lippincott Co., Philadelphia, 1936.*)

In this book, an effort is made to correlate pathological findings in the thyroid gland with abnormal clinical states. The author frankly and frequently admits our ignorance about many fundamental facts. In Chapter I, he says: "It is becoming more and more obvious that what we have assumed to be knowledge is appallingly dubitative. We do not know whether, once we have grown up, the thyroid gland be friend or enemy.".... "My suspicion is that the thyroid gland, by throwing its gears in reverse, sees to our orderly demise, unless some intercurrent disease or mechanical contrivance anticipates its design.". . . . "Only recently have we learned that the goiter degenerates, leading to a cardiac death."

About myxedema he says: "In other words myxedema, like hyperthyroidism, is due to some deleterious secretion and not to a cessation of function as commonly believed."

One of his main theses is explained by the following quotation: "Lest I forget to do so, I may say at the outset the idea is to emphasize the fact that goiter, whatever the type in the beginning, is a continuous process ending in a cardiotoxic state."

About non-toxic goitres, he says: "It is necessary to note this fact because a bosselated goiter is cardiotoxic from the start though many years may elapse before it forces itself on our attention as definite cardiac failure.". . . . "It is bosselated because these new acini have formed and it is these rather than the accumulation of colloid in the individual acini that are responsible for the increase in size."

About toxic nodular goitre, he says: "Usually when a nodular nontoxic goiter becomes toxic, there is no epithelial hyperplasia and the pathologist despairs. The fact is, in the majority of cases there is no hyperplasia. It is a toxicity of degeneration. If one studies these goiters carefully the colloid is found to have become basophilic, the cells flat, the nuclei stain variously and in many the connective tissue has undergone change. The patient is sick and there is no evidence of cellular hyperplasia, but there is abundant evidence of degeneration. One is compelled to say that it is a toxicity of degeneration."

The text is liberally illustrated by photographs of patients, gross specimens, and microphotographs. But the more one studies the pictures, the less one is convinced by the text. Most of the author's ideas on the pathology of the thyroid gland come directly from Wilson, from whom he quotes liberally and says about one of his papers: "The paper thoroughly impressed me with the fact that in goiter, as well as all other diseases, there must be a relation between the pathology and the clinical manifestation. In fact this book is dedicated to an effort to demonstrate that relationship." At the end of each chapter three or four references are critically discussed in fine print. Here the author presents what he considers the attitude of a surgeon toward the various phases of laboratory investigation of thyroid disease. In speaking, for instance, of the fact that in the course of the Aschheim-Zondeck Test, the thyroid gland of a rabbit has been noted to show proliferation of epithelium of the acinal cells after the injection of urine from pregnant women, he says: "The moral is rabbits should avoid the urine of pregnant women."

In discussing the wax reconstruction models of the thyroid gland, made by Rienhoff, he says: "Valuable as reconstructions are, the method is too crude to show cytologic detail. Structures this method does not show must not be declared to be nonexistent but that the models do not show them."

When the book is finished, one must confess to a great confusion. If the reviewer were to adopt the style of the author, he might say: "The moral is: Internists should avoid books on 'Surgical Pathology'."

H. M. T., Jr.

Treatment in Psychiatry. By OSKAR DIETHELM. 476 pages. $4.00. (*The Macmillan Company, New York, 1936.*)

Dr. Diethelm has given us a comprehensive treatise on treatment which will be valued by psychiatrists, physicians in general, and medical students. The presentation is clear and factual and based on sound common sense. It takes therapy out of the realm of art and intuition and makes of it a real scientific procedure.

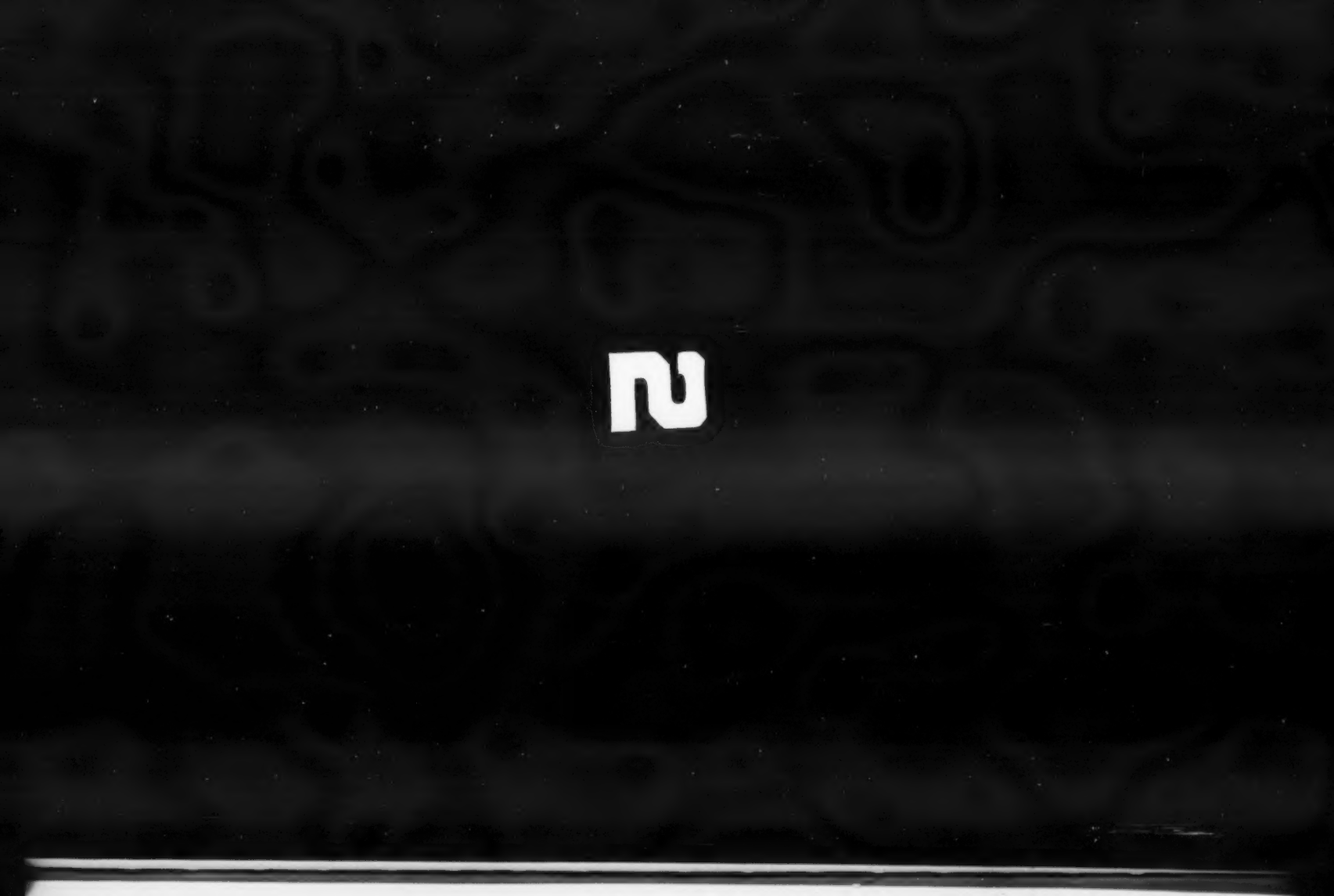
The basis of treatment lies in the psychobiological understanding of the human personality. The human being is an integrate: a ceaseless interplay and interrelation of all his functions of which the mental functions are only a special variety. Thus, psychiatric treatment is concerned with all the functions, and seeks its point of attack at any level of integration, physiological as well as "mental." Man is seen as a person possessing a life history, who functions with symbolization. The therapist must be prepared to deal with past experiences as well as anticipations, scrutinizing the life record for its phases of development and moving toward a synthesis of conflicting components.

A great virtue of the book lies in its inclusiveness. Introductory material adequately presents various "schools" of psychoanalytic and psychiatric thought. Special methods of investigation and treatment, such as suggestion, hypnosis, persuasion, re-education, and psycho-analysis are explained. Most of the material for this book came from Dr. Diethelm's own experiences in therapy, and is founded upon Meyerian principles of distributive analysis and synthesis; *i.e.*, a comprehensive study of all the components of personality: the life record, the blending of conation and cognition as topically, and emotions as diffusely regulative emphases, rather than as detachable components; the range of attention, endurance; familial and social relations, the sexual life and development, assets and liabilities; subject-organization of the moment and personality-organization of the lifetime. The author remains free of any prejudicial separation of body, mind and soul. The aim is to reduce the facts of the story to terms of an understandable experiment of nature and to correct those factors which have gone wrong in producing the illness.

Subsequent chapters present in detail the therapy of excitements, depression, schizophrenic relations, delirious conditions and organic psychoses, stressing the rôle of the physician in psychotherapy, as well as the aids to be had from occupational therapy, drug therapy, socialization, *et cetera*. The chapters on the psychoneuroses, alcoholism, drug addiction, sexual difficulties, and motor neuroses should give the non-psychiatric practitioner a real basis for the treatment of common psychoneurotic conditions.

The book retains practicality because therapy is discussed always with reference to actual case histories. This is a much-needed book and one that can be recommended whole-heartedly. It should be in the library of all psychiatrists and all others who wish to see what a modern constructive, optimistic therapeutic program can accomplish.

T. A. C. R.



THE OCCURRENCE OF NON-HAEMOGLOBIN IRON IN WHOLE BLOOD

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Up to recent times it had been generally believed that the only iron in the blood not combined with haemoglobin was the very small amount in the serum. Following the work of Butterfield (1) and of Peters (2) it has come to be generally accepted that haemoglobin has a definite content of iron, namely 0.34 per cent, so that on numerous occasions it has been proposed to use the determination of iron as a means of estimating haemoglobin where great accuracy is desired. Since the introduction of simple and accurate methods for the determination of iron during the last twenty years, numerous comparisons between the iron of the blood and that of the haemoglobin determined by a variety of methods have been carried out (3). In general, agreement has been found between the iron actually determined and that calculated from the haemoglobin. As a result of these reports Van Slyke and Peters in their recent book on biochemical methods advance the possibility of using the determination of iron as an alternative method to that of oxygen capacity for standardizing the clinical estimation of haemoglobin.

As far back as 1912 Fowell (4) compared iron and haemoglobin in blood obtained from normal persons and patients suffering from various forms of anaemia. He found that in the normal and in "secondary" anaemia the two values corresponded, but that in pernicious anaemia the value for iron in the blood exceeded that calculated from the haemoglobin by amounts varying from five to thirteen milligrams. Even earlier than this there had been found discrepancies between haemoglobin calculated from the total iron and haemoglobin

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estimated by colorimetric procedures, but the methods were too inaccurate and the normal variation too great to lead to any confidence in the results. Lately Domenici (5) confirmed Fowell's findings.

Barkan (6), Lintzel (7) and Starkenstein (8), independently of each other and using different methods, demonstrated in blood the existence of iron that could be freed by digestion with HCl. This "inorganic" or "easily-split" iron averaged about 1.7 mg. per 100 cc. under all conditions. It occurred within the red corpuscles and was found to bear no relation to the iron of the serum which varies between 0.1 and 0.2 mg. per 100 cc.

One of us (9) in a recent publication reported the results of a comparison between the iron of the blood determined by analysis and that calculated from haemoglobin estimated by the Newcomer method. In general, agreement was found, but under certain conditions the total iron (by analysis) exceeded the "haemoglobin" iron by significant amounts. These conditions were:—(1) the first two months of life during which the non-haemoglobin iron amounted in some instances to more than 20 mgs. per 100 cc.; (2) during administration of iron; (3) in two cases of infection.

There are then three forms in which iron occurs in the blood in addition to its combination with haemoglobin. (1) The iron of the serum in very minute amounts (0.1–0.2 mg. per 100 cc.). (2) The "inorganic" or "easily-split" (*leicht abspaltbares*) iron, occurring in the red corpuscles and amounting to between 1 and 2 mg. per 100 cc. whole blood. This form is present in all blood but would not be manifest in a comparison between iron and haemoglobin, since it lies within the combined "errors" of the methods. (3) A form occurring also within the red corpuscles, probably absent or present only in very small amounts in most blood, but increased in the conditions enumerated above. The purpose of the work reported here is an investigation of this latter form of iron.

METHODS AND MATERIAL

The plan of study was essentially a comparison of oxygen capacity, haemoglobin by the Newcomer method, total iron of the blood, and "easily-split" or "inorganic" iron determined by Starkenstein's method, all determinations made on the same sample of oxalated blood obtained by venipuncture. The purpose was to confirm former observations as well as to find out whether the iron-containing substance was capable of carrying oxygen and, if possible, its relation to formation or destruc-

tion of haemoglobin. The blood samples were obtained from infants and children on the wards of the Harriet Lane Home.

The method for oxygen capacity and the Newcomer method for haemoglobin need no description. The total iron of the blood was determined on 0.1 cc. samples by the method previously described (ashing with perchloric-sulphuric acid mixture, colorimetric determination by thiocyanate-amyl-alcohol method). For determination of "inorganic" iron 1 cc. of blood was digested on the steam bath for one half an hour with 5 cc. 2.5 N·HCl· precipitated with trichloracetic acid, centrifuged and the supernatent fluid analyzed for iron colorimetrically.

RESULTS

1. Comparison of haemoglobin determined by oxygen capacity and by the Newcomer method. This comparison is made in columns 6, 7 and 8 of Tables 1a, 1b and 1c. The magnitude of the "error" is represented in chart 1 as a distribution curve. As may be seen, 61 out of 74 or about five-sixths of the figures corresponded within 12 per cent. This "error" is no greater than that obtained by others who have reported comparisons between the two methods. In about 10 per cent of the determination the values for haemoglobin obtained by the Newcomer method exceeded those calculated from oxygen capacity by more than 20 per cent. The only reason for attaching any significance to these aberrant values is that they all occurred either in babies under two months of age, or in those receiving iron—two of the conditions in which there are also likely to be excessive amounts of "non-haemoglobin" iron. Although the figures are no more than suggestive, since the "error" of the methods is such that they might fall within the limits of coincidence, they nevertheless do raise the question of the presence of some pigment other than haemoglobin in the blood under certain conditions.

2. Comparison of the total iron of the blood with "haemoglobin iron" calculated from oxygen capacity[1] (columns 9, 10 and 11, Table 1).

[1] 100 gms. of haemoglobin contain 340 mgs. iron on the basis of the determinations of Butterfield and of Peters. Therefore, the iron combined with haemoglobin expressed in mgs. per 100 cc. can be calculated by multiplying the haemoglobin in gms. per 100 cc. by 3.4. It is true that this figure is only an average and depends on the degree of purity of the haemoglobin samples analyzed. On the other hand, the fact that the value for haemoglobin determined by oxygen capacity coincides with that calculated from the iron content of the whole blood under ordinary conditions confirms the essential correctness of the figure.

TABLE 1

Comparison of Haemoglobin by O_2 capacity and Newcomer methods and of total iron (by analysis) with Haemoglobin iron (calculated from O_2 capacity)

NAME	AGE	DIAGNOSIS	O_2 CAPACITY	NEWCOMER READING	HAEMOGLOBIN			IRON			EASILY SPLIT IRON
					O_2 capacity	Newcomer	Deviation	Total by analysis	Calculated from O_2 capacity	Difference	
Table 1a. Under one year											
					gms. per 100 cc.	*gms. per 100 cc.*	*per cent*	*mgs. per 100 cc.*	*mgs. per 100 cc.*		
Br.	6 w	Normal	14.1	10.9	10.5	9.8	−6.7	55.4	35.7	+19.7	1.7
Co.	7 w	Harelip	16.2	8.0	12.1	13.4	+10.7	39.7	41.1	1.4	
Yo.	7 w	Prematurity	12.8	10.3	9.6	10.4	+8.3	62.8	32.6	+30.2	1.7
Co.	7 w	Prematurity	11.0	10.6	8.2	10.1	+23.2	51.6	27.9	+23.7	
Bo.	2 m	Mild infection	13.1	11.0	9.8	9.7	−1.0	38.4	33.3	+5.1	
Al.	2 m	Prematurity	15.4	9.3	11.5	11.5	0	35.8	38.8	−3.0	1.3
Me.	2 m	Diarrhea	15.8	9.3	11.8	11.5	+2.5	39.7	40.1	−0.4	1.2
Pa.	2 m	Prematurity	11.1	13.6	8.0	7.9	−1.2	24.4	27.2	−2.8	1.1
Cr.	2½ m	Normal	14.6	10.2	10.9	10.5	−3.7	34.8	37.1	−2.3	2.3
Ho.	2½ m	Prematurity	10.5	13.1	7.8	8.2	+5.1	34.8	26.5	+8.3	0.9
Mi.	2½ m	Infection	13.0	13.0	9.6	8.3	−13.5	35.1	33.0	+2.1	
Ma.	3 m	Diarrhea	15.2	9.8	11.3	10.9	−3.5	52.8	38.4	+14.4	1.7
"			15.6	12.4	11.6	8.6	−26	45.1	39.5	+5.6	
Da.	3 m	Cirrhosis of liver	13.3	11.0	9.9	9.7	−2.0	42.7	33.6	+9.1	0.7
Hu.	4 m	Normal	12.7	11.4	9.5	9.4	−1.1	32.3	32.3	0	1.2
Go.	4 m	Pneumonia	7.6	19.2	5.8	5.6	−3.4	17.2	19.4	−2.2	1.6
Ja.	6 m	Normal	9.8	13.5	7.3	7.9	+8.2	26.9	24.8	+2.1	0.8
Fo.	7 m	Diarrhea. Mild infection	9.9	14.1	7.4	7.6	+2.7	35.2	25.0	+10.2	

			6.7?	14.3	5.0?	7.5	+50?	38.8	17.0	+21.8	1.8	Fe 10 days
			11.6	11.3	8.7	9.5	+9.1	30.6	29.6	+1.0	0.4	Fe 14 days
Co.	8 m	Sickle cell anemia	5.6	21.7	4.2	4.9	+16.6	14.4	13.9	+0.5		Jaundice
Yo.	9 m	Haemolytic anemia	12.9	10.7	9.6	10.0	+4.2	32.4	32.6	−0.2		
Si.	9 m	Arthritis	15.1	9.5	11.3	11.3	0	41.8	38.5	+3.3	0.6	
Sm.	9 m	Scurvy	10.8	10.6	8.1	10.1	+24.7	53.8	27.5	+26.3	1.7	
Hu.	10 m	Rickets anemia	12.0		9.0			35.8	30.6	+5.2		
			13.1	10.0	9.8	10.7	+9.2	35.8	33.3	+2.5	1.8	Fe 3 days
Br.	12 m	Otitis media	11.1	10.2	8.3	10.5	+27	39.7	28.2	+11.5	0.7	

Table 1b. One to three years

Cu	13 m	Normal	15.6	8.6	11.6	12.4	+6.9	38.7	39.4	−0.7	1.0	
Fi	13 m	Cleft palate	10.8	12.5	8.0	8.6	+7.5	33.1	27.2	+5.9	1.8	
"			11.2	12.5	8.3	8.6	+3.6	35.2	28.4	+6.8	2.7	Fe 3 days
"			12.2	12.8	9.1	8.4	−7.7	52.2	31.0	+21.2		Fe 7 days
Ma	13 m	Convalescent from pneumonia	9.6	15.3	7.1	7.0	−1.4	20.8	24.2	−3.4	0.4	
"			9.8	14.3	7.3	7.5	−2.7	25.9	24.8	+1.1	3.0	Fe 2 days
"			11.5	12.8	8.6	8.4	−2.3	39.7	29.2	+10.5	1.0	Fe 6 days
Ve	14 m	Otitis media. Convalescent from pneumonia	9.7		7.2			31.0	24.5	+6.5	1.4	
"			12.9	9.0	9.7	11.9	+2.3	43.5	33.0	+10.5	0.5	Fe 10 days
"			13.5	9.8	10.1	10.9	+7.9	41.4	34.3	+7.1	2.5	Fe 14 days
Si	15 m	Rickets. Scurvy	12.6	10.1	9.4	10.6	+12.8	29.8	31.9	−2.9	1.4	
McC	16 m	Cretinism	10.8	14.4	8.0	7.5	−6.2	29.0	27.2	+1.8		
Do	17 m	Pneumonia	13.1		9.8			34.4	33.4	+1.0		
"		Convalescent	11.0	11.4	8.1	9.3	+14.8	35.5	27.6	+7.9	1.9	
Ha	18 m	Malnutrition. Pyelonephritis	8.8	13.6	6.6	7.8	+18.2	19.8	22.4	−2.6	1.1	

TABLE 1—*Concluded*

NAME	AGE	DIAGNOSIS	O_2 CAPACITY	NEWCOMER READING	HAEMOGLOBIN			IRON			EASILY SPLIT IRON	
					O_2 capacity	Newcomer	Deviation	Total by analysis	Calculated from O_2 capacity	Difference		
Table 1b. One to three years—*Concluded*												
					gms. per 100 cc.	*gms. per 100 cc.*	*per cent*	*mgs. per 100 cc.*	*mgs. per 100 cc.*			
Ha			9.2	11.2	6.9	9.5	+38	22.7	23.4	−0.7	2.6	Fe + Cu 4 days
"			11.2	13.4	8.4	8.0	−4.8	24.1	28.5	−4.4	1.8	Fe + Cu 7 days
Wi	20 m		9.1		6.8			25.3	24.1	+1.2		
Fi	2 y	Pneumonia	13.1	11.0	9.8	9.7	−1.0	32.0	32.9	−0.9	1.6	
"			14.4	10.6	10.7	10.1	−5.6	30.4	35.2	−4.8	2.1	Fe + Cu 3 days
"			15.3	10.0	11.4	10.7	−2.6	35.0	38.8	−3.8	1.3	Fe + Cu 6 days
Eh	2 y	Sepsis	14.0	10.7	10.4	10.0	−3.8	27.6	35.4	−7.8	1.1	
Fr	2 y	Pleural effusion	13.6	11.1	10.2	9.7	−4.9	31.4	34.7	−3.3		
"			11.2	11.9	8.4	9.0	+7.1	35.0	28.5	+6.5	1.2	
Cz	2½ y	Empyema	15.1	8.7	11.3	12.3	+8.8	47.9	38.4	+9.5	1.6	
Gl	3 y	Sarcoma	11.8	12.0	8.8	8.9	+1.1	30.7	29.9	+0.8		
Br	3 y	Typhoid	14.8	8.7	11.5	12.3	+6.9	47.9	39.2	+8.7	1.5	
Table 1c. Over four years												
Wa	4 y	Leukaemia	14.8	10.9	11.0	9.8	−11.0	35.2	37.4	−2.2	1.1	
"			9.6	14.7	7.2	7.3	+1.4	29.4	24.5	+4.9	0.9	
Ba	4 y	Eczema	7.9	17.6	5.9	6.1	+3.4	19.1	20.0	−0.9	1.7	
Fi	4 y	Nephritis	14.9	9.7	11.1	11.0	−0.9	34.4	37.9	−3.5	0.7	
"			17.1	8.3	12.7	12.9	+1.6	43.2	42.3	+0.9	1.2	Fe + Cu 6 days
Br	5 y	Pneumonia	8.2	14.5	6.1	7.4	+2.1	25.7	20.8	+4.9	1.0	

Hu	5 y	Lead poisoning	10.3	14.5	7.7	7.4	−3.9	34.4	26.2	+8.2	0.9	
Ho	5 y	Lead poisoning	15.6	9.7	11.6	11.0	−5.2	40.4	39.6	+0.8	1.1	
Si	7 y	Sarcoma	16.5	9.3	12.3	11.5	−6.5	42.2	41.9	+0.3	1.7	
"			17.9	8.6	13.4	12.5	−6.7	33.8	45.5	−11.7	1.2	Fe 3 days
"			16.3	8.7	12.2	12.3	+0.8	43.8	41.4	+2.4	1.2	Fe 6 days
Ca	8 y	Myxedema	16.0	8.8	11.9	12.2	+2.5	57.2	40.6	+16.6	1.6	
La	8½ y	Lung abscess	13.1	11.4	9.8	9.4	−4.1	34.4	33.2	+1.2	1.3	
"			14.8	11.0	11.0	9.7	−11.8	38.4	37.6	+0.8	1.6	
"			14.6	9.8	10.9	10.9	0	38.1	37.1	+1.0	1.3	
Del	9 y	Sepsis	15.5	9.1	11.6	11.8	+1.7	40.7	39.3	+1.4	1.5	
"			15.6	8.9	11.7	12.0	+2.6	40.7	39.6	+1.1	1.1	Fe 3 days
"			17.6	7.9	13.1	13.5	+3.1	42.2	44.6	−2.4	1.1	Fe 6 days
Co	10 y	Bronchiectasis	17.2	9.4	12.8	11.4	−11.0	34.8	43.5	−8.7	1.1	
"			18.1	8.5	13.5	12.6	−6.7	43.3	45.9	−2.6	1.3	Fe + Cu 5 days
Wo	10 y	Leukemia	10.2	14.3	7.6	7.5	−1.3	25.2	25.9	−0.7	1.6	
Mo	12 y	Rheumatic fever	17.0	8.7	12.7	12.3	−3.4	51.2	43.3	+7.9	1.4	
"			16.8	9.4	12.5	11.4	−8.8	35.7	42.6	−6.9	1.2	Fe 4 days
"			18.6	7.7	13.9	13.9	0	49.9	47.2	+2.7	1.4	Fe 6 days

The difference between "haemoglobin iron" and total iron of the blood is represented in chart 2 as a distribution curve. The normal limit of variation is considered to be ±6 mgs. Naturally a few values lying outside this limit will have no significance, but the number of cases in which the total iron exceeds the "haemoglobin iron" by more

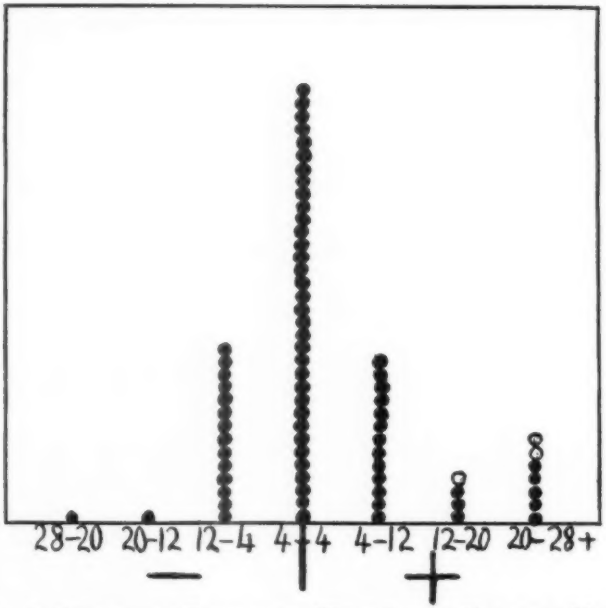

CHART 1. DISTRIBUTION CURVE OF THE "ERROR" OF THE NEWCOMER METHOD

Note. The O_2 capacity is used here as the standard, so that the "error" is obtained by the formula $100\left[\frac{\text{Hgb. (Newcomer)}}{\text{Hgb. } O_2 \text{ capacity}} - 1\right]$

(Column 8: Table 1.)

than 6 mgs. per 100 cc. is too great to be explained on the basis of chance. Of the twelve figures lying above 10 mg., four occurred in normal infants up to three months of age, four in infants of less than eighteen months receiving iron, two in infants suffering from infection, one in an infant with scurvy and one in a child of eight years with myxedema.

Of the values lying between 8 and 10 mgs., one occurred in a premature baby of two and a half months, one in an infant of three months with cirrhosis of the liver, three in children with infections and one in a child of five years with lead poisoning.

SPECIAL CONDITIONS REPRESENTED

Infection. Of the children with infection, relatively few had "non-haemoglobin" iron values above 8 mgs. per 100 cc., in all not more

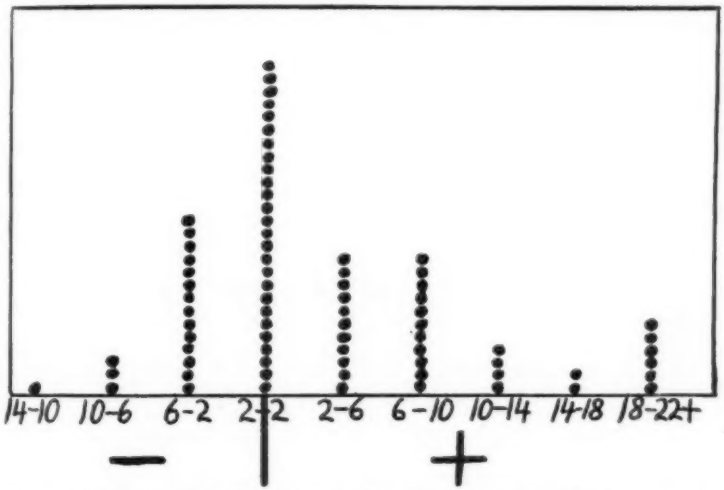

CHART 2. DISTRIBUTION CURVE OF THE DIFFERENCE BETWEEN TOTAL IRON (BY ANALYSIS) AND HAEMOGLOBIN IRON (CALCULATED FROM O_2 CAPACITY). (COLUMN 11: TABLE 1)

than four out of thirteen, and of these none were over three years of age.

Anemia. No child with a haemoglobin of less than 8 gms. per 100 cc. had "non-haemoglobin" iron of more than 8 mgs. per 100 cc. unless he were receiving iron. This result is in accord with that of the figures previously reported and with those in the literature with the exception of those for pernicious anaemia. In two cases of leukaemia the total iron corresponded with the haemoglobin iron. Also in two cases with excessive haemolysis and a high reticulocyte count, the

TABLE 2

Effect of iron administration on non-haemoglobin iron of the blood

Note: The data on which this table is constructed have been taken from previous work in which the "haemoglobin iron" was calculated from the haemoglobin estimated by the Newcomer method. The determinations were made every three or four days—a frequency that would be impracticable if oxygen capacity determinations were made the basis for haemoglobin estimation as in the present work.

	DAYS AFTER BEGINNING IRON ADMINISTRATION							
	0–5	5–10	10–15	15–20	20–25	25–30	30–35	35–40
Daily rise in hgb., gms. per 100 cc.	0.27	0.25	0.20	0.15	0.18	0.05	0.05	0.12
Non-hgb. iron, mgs. per 100 cc.	1.7	3.1	9.8	10.3	12.5	8.6 Cu	12.6 Cu	6.5 Cu
Rise in hgb.	0.30	0.27	0.20	0.15	0.20	0	0.17	0
Non-hgb. iron	1.8	0.9	6.9	5.4	3.2	8.5	12.7	9.3 Cu
Rise in hgb.	0.12	0.17	0.27	0.27	0.05	0.27	0.07	
Non-hgb. iron	2.1 Cu	2.0 Cu	4.7 Cu	3.6 Cu	4.5 Cu	8.2 Cu	6.5 Cu	
Rise in hgb.	0.12	0.20	0.10	0.04	0	0.05	0.10	
Non-hgb. iron	5.2	9.3	9.4	9.9	8.0	6.2	11.5 Cu	
Rise in hgb.	0.15	0.35	0.25	0.10	0.10	0.30		
Non-hgb. iron	1.1	1.3	1.0	1.0	1.8	1.1 Cu		
Rise in hgb.	0.26	0.10	0	0.05	0.04			
Non-hgb. iron	3.0	3.0	7.1	3.0	5.5 Cu			
Rise in hgb.	0.17	0.25	0.14	0.04				
Non-hgb. iron	1.0	1.5	1.2	6.0 Cu				
Rise in hgb.	0.21	0.28	0.20					
Non-hgb. iron	0.0	2.0	1.0 Cu					
Rise in hgb.	0	0.1	0.30					
Non-hgb. iron	4.0	—	6.0 Cu					
Rise in hgb.	0.07	0	0.12					
Non-hgb. iron	2.0	6.5	4.0					

total iron did not exceed the haemoglobin iron. To these may be added a case of sickle cell anaemia with high urobilin excretion and reticulocyte count from the previous series.

Early infancy. Three out of four infants under two months of age had the "extra" iron in the blood in large amounts. This is in accord with the previously published figures, and is also indicated by those of Kotikoff (11), although he did not actually compare iron and haemoglobin in the same infants. Abt (12) has also observed the presence of "extra" iron in the blood in a group of premature infants.

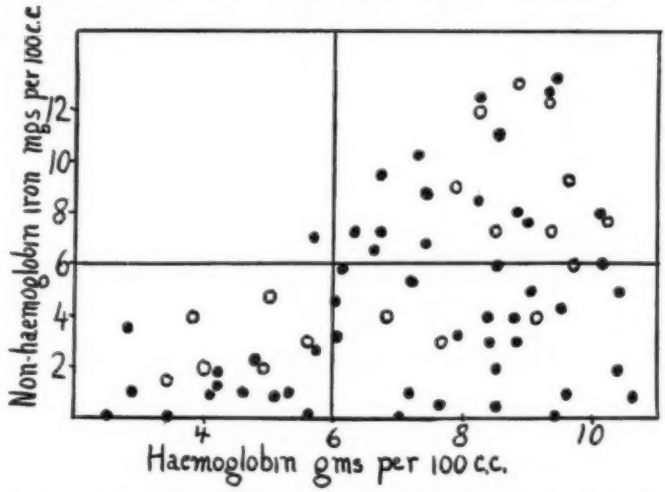

CHART 3. TO SHOW RELATION OF "NON-HAEMOGLOBIN" IRON TO HAEMOGLOBIN PERCENTAGE IN CASES RECEIVING IRON

During administration of iron. The effect of iron in raising the "non-haemoglobin" iron of the blood was confined to infancy, although it is possible that with a larger series in older children and more prolonged administration there might have been found a few cases in later childhood with increase in "non-haemoglobin" iron.

In studying the effect of iron administration in infancy, we may make use of the figures previously reported. Since all determinations in the previous work were made on blood obtained from a small stab in the skin, it was possible to carry out comparisons at frequent inter-

vals, a procedure not feasible in the present series in which the blood was obtained by venipuncture.

In Table 2 are contained the figures for "non-haemoglobin" iron. The vertical columns of this table represent five day periods following the commencement of iron administration. Ferric ammonium citrate was given by mouth in ten per cent solution, 2 cc. per kilogram of body

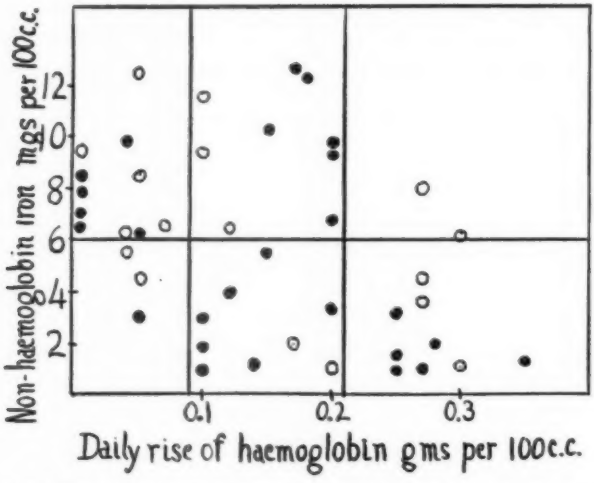

CHART 4. TO SHOW RELATION OF "NON-HAEMOGLOBIN" IRON TO RATE OF RISE IN HAEMOGLOBIN

Note. The chart has been divided by vertical lines into three divisions corresponding to slow, moderate, and rapid rise in haemoglobin. The solid circles represent cases receiving iron alone, the hollow circles those receiving copper in addition to iron. The line drawn at 6 mgs. represents the upper limit of "normal variation." This dividing line between the "probably normal" and the "probably abnormal" has been chosen as a result of over two hundred determinations of "non-haemoglobin" iron (See also Chart 2).

weight per day. The table contains, in addition to the figures for "non-haemoglobin" iron, also figures representing the daily rise in haemoglobin expressed in grams per 100 cc. of blood during the five day period.

From this table it may be seen that there was no rise in "non-haemoglobin" iron within the first five day period. After the fifth

day, however, there occurred at some time in the course of iron administration in the majority a rise in the "non-haemoglobin" iron, which in a few cases tended to remain elevated over a considerable time. In chart 3 the "non-haemoglobin" iron is plotted against the haemoglobin, and in chart 4 against the rate of rise in haemoglobin. From chart 3 it is clear that the higher the haemoglobin the greater the tendency to high values for "non-haemoglobin" iron. Chart 4 offers a possible explanation for this, as it may be seen that when the haemoglobin is rising rapidly there is little tendency for "non-haemoglobin" iron values to rise above 6 mgs. per 100 cc., whereas when the haemoglobin is rising slowly—less than 0.1 gm. per 100 cc. per day—the majority of the values lie above 6 mgs. (The figures obtained during the first five days of iron administration were not used in constructing this chart.) It is of course a common observation that the haemoglobin tends to rise more rapidly at the beginning of treatment in anaemia, while the haemoglobin is lower than later when it is approaching a normal value.

The hollow circles represent values obtained during administration of copper in addition to iron. One cannot draw conclusions from a series as small as this, but it may be of significance that, while the haemoglobin was rising rapidly, higher values for non-haemoglobin iron were obtained during administration of copper.

DISCUSSION

The discrepancy between total iron and "haemoglobin" iron allows of two interpretations: (1) that a compound exists in which iron is tightly bound to the molecule, but which cannot be considered haemoglobin because it does not carry oxygen; (2) that under certain conditions a form of haemoglobin exists which contains a higher percentage of iron than that ordinarily found; possibly a more primitive form. There is nothing in this work which can aid in deciding which of these interpretations is correct, except that the occurrence of the "extra" iron during iron therapy after the haemoglobin has risen suggests that the former of the two hypotheses is the correct one. On the other hand one may speculate that its presence in pernicious anemia might depend on a more primitive form of haemoglobin coinciding with the more primitive form of blood formation occurring in that disease.

The majority of the conditions under which the "extra" iron occurs have in common an increased rate of haemoglobin metabolism, either formation or breakdown. It is therefore reasonable to suppose that it may be associated with an intermediate product in the formation or breakdown of haemoglobin. On the other hand the "extra" iron was not found in three cases of hemolytic anemia in which the rate of formation and breakdown was ten to twenty times the normal. At the present stage of the investigation further speculation is unprofitable.

It was not feasible to attempt iron determination in the plasma in such small babies. Since determinations on plasma carried out by others have invariably, as far as our knowledge goes, shown an iron content below 0.2 mg. per 100 cc., it is presumed that the "extra" iron exists within the red cells. That it has nothing to do with reticular or nuclear substance is shown by its absence in three cases of hemolytic anemia and two cases of leukaemia.

SUMMARY

Normally the total iron of the blood corresponded with that calculated from haemoglobin within a limit of ±6 mg. per 100 cc. Under certain conditions the total iron was found to exceed the haemoglobin iron by more than 6 mgs. per 100 cc. These conditions were: (1) The first two months of life; (2) During iron therapy up to the end of the second year of life; (3) During infections. In addition, an increase in non-haemoglobin iron was found in a few isolated cases (scurvy, 1 case; lead poisoning, 1 case; myxedema, 1 case; cirrhosis of the liver, 1 case). As pointed out by Starkenstein and others, iron exists in the red cells in a combination from which it can be easily split by HCl. This form probably accounts for most of the non-haemoglobin iron occurring normally, amounting to between 1 and 2 mgs. per 100 cc. It is, however, not increased with increase in the total iron in the conditions named above, so that iron in these conditions exists in a so-called "organic form." Its significance is not clear. Two possible interpretations may be advanced. (1) It represents a possibly more primitive form of haemoglobin having a higher content of iron than is present ordinarily. (2) It represents an iron-containing organic compound which does not carry oxygen, and may possibly represent

an intermediate product in the formation and breakdown of haemoglobin.

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PERENNIAL ALLERGIC RHINITIS: AN ANALYSIS OF ONE HUNDRED AND NINETY-EIGHT CASES

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Perennial hay-fever is now a well recognized disease. Coincidently with the great advances made in our knowledge of allergic states during the past twenty years it has gradually emerged as a definite and important manifestation of hypersensitivity. It has, however, masqueraded under several descriptive but non-pathognomic terms—vasomotor, hyperesthetic, hyperplastic and more recently atopic or allergic rhinitis. Unlike seasonal pollen hay-fever, not all cases of perennial rhinitis are due to specific hypersensitivity, and it is important for the sake of clarity, and for aid in distinguishing the various forms, that the diagnosis of perennial *allergic* rhinitis be applied only to cases of individuals suffering from contact with one or more proven allergic irritants. Many other cases of perennial rhinitis are more nearly related to infections, climatic conditions and metabolic or psychic disturbances, but more study and data are required to differentiate clearly between these types.

Despite the profound interest in allergic conditions exhibited by the profession, most of the reports on perennial allergic rhinitis have been brief, in contrast to the numerous and detailed treatises on seasonal hay-fever, and furthermore have covered only a short period of observation.[1] Hansel (1), Walker (2), Rich (3), Spain (4), Vaughan (5), Rowe (6), Eyermann (7), Rackemann (8), and Balyeat (9) have contributed to our knowledge of allergic rhinitis, but with the exception of the reports by Rackemann (8) detailed results of treatment in

[1] For historical, immunological and pathological details reference may be made to several excellent textbooks: *Clinical Allergy.* By F. M. Rackemann, (The Macmillan Co., New York, 1931); *Asthma and Hay-Fever.* By Coca, Walzer and Thommen, (C. C. Thomas, 1931); *Allergy of the Nose and Paranasal Sinuses.* By F. K. Hansel, (C. V. Mosby Co., 1936).

a large series of cases followed for a long period of time are lacking. It is generally believed that a great variety of substances, such as various house and occupational dusts, animal danders, feathers and cosmetics are the most frequent inciters of the disease, but some difference of opinion exists as to whether ingested foods are causative factors. For more than a decade, treatment by *desensitization* has been widely employed, but during the past few years *ionization* of the nasal mucosa has gained many adherents, especially among the laryngologists. Observations on this procedure cover, unfortunately, too short a span of time to permit of definite conclusions as to its value. The majority opinion holds, however, that the method is valueless in seasonal hay-fever and in perennial rhinitis in which specific hypersensitivity can be demonstrated.[2]

In the present paper, we wish to present an analysis of the data obtained on 198 cases of perennial allergic rhinitis encountered in private practice. The observations cover a period of from 1 to 10 years. In addition to a study of the allergic factors, the majority of the patients were subjected to a complete diagnostic survey, including frequent examinations by specialists on diseases of the nose and throat. (It may be stated that most of our patients had had routine nose and throat examinations prior to our own observations.) Skin reactions were determined by the intradermal technique. In many cases the passive transfer procedure of Prausnitz-Küstner was also carried out. Studies of nasal smears for eosinophiles were not made. Only after close scrutiny of the history, the pertinent clinical data and the skin reactions, was a diagnosis made and conclusions drawn as to the causative factors.

It may not be amiss at this time to call attention to several general aspects of this affliction which has been and probably is still looked upon by the medical profession at large as a minor medical ailment. This conception is correct only when the symptoms are mild and episodic; when they are severe and persistent the patients suffer greatly, and enjoy only rare and brief intervals of comfort. In such sufferers a lowered state of well being commonly develops, and serious

[2] For recent review of the Ionization treatment of Allergic Rhinitis see F. K. Hansel's *Allergy of the Nose and Paranasal Sinuses*, page 635. (C. V. Mosby Co., St. Louis, Mo. 1936.)

mental depression may sometimes occur. In addition, complications such as infections of the paranasal sinuses, either acute or chronic, are common, and the development of other allergic manifestations, asthma or pollen hay-fever, is frequent and renders treatment more difficult. For this reason in dealing with individuals who are liable to develop perennial allergic rhinitis, the hazards from smoke and dust inherent in cities and industrial centers must, as far as possible, be restricted.

AGE AND SEX DISTRIBUTION IN PERENNIAL ALLERGIC RHINITIS

The age and sex distribution of 198 cases of perennial allergic rhinitis are given in Table I. The disease is not confined to any

TABLE I

Age and sex distribution in 198 cases perennial allergic rhinitis

AGE IN DECADES AT ONSET	NUMBER OF PATIENTS	SEX DISTRIBUTION	
		Male	Female
1–10	54	32	22
11–20	36	15	21
21–30	42	14	28
31–40	42	14	28
41–50	15	3	12
51–60	6	4	2
61–70	3	1	2

particular age group; it has been more frequently encountered in young than in old individuals, and is especially common before the age of 10 years. A definite but slight preponderance of males holds during the first decade, but thereafter the females predominate.

INCIDENCE OF ALLERGY IN FAMILY HISTORY, EOSINOPHILIA AND ASSOCIATED ALLERGIC DISEASES

Table II gives the incidence of a family history positive for allergy, eosinophilia, and other allergic manifestations encountered in this series. Less than one half of the patients presented a positive family history either on the maternal or the paternal side. This is lower than the incidence encountered in pollen hay-fever and it may represent a fundamental point of difference between these two dis-

eases, which in other respects are so similar. Only 12 per cent of 100 patients on whom blood studies were made showed an eosinophilia, when 500 eosinophiles per cubic millimeter of blood were taken as the normal maximum. This was true despite the presence of asthmatic symptoms, in which eosinophilia is so frequently observed. Of the associated manifestations of allergy, asthma was present in 25 per cent; pollen hay-fever in 20 per cent; eczema in 5 per cent; urticaria in 3 per cent and food sensitivity in less than 2 per cent. Almost 50 per cent of these various forms of hypersensitivity made their appearance during the first decade of life; hence, when the rhinitis begins after the first decade, it is improbable that the individual will subsequently develop other allergic disease.

TABLE II

Incidence of positive family history, eosinophilia, associated allergy

AGE IN DECADES	NUMBER OF PATIENTS	FAMILY HISTORY OF ALLERGY	EOSINOPHILIA (100 PTS.*)	ASSOCIATED ALLERGIC DISEASE				
				Asthma	Eczema	Urticaria	Hay fever	Food sensitivity
1–10	54	41	5	25	6	2	11	2
11–20	36	9	0	4	1		11	
21–30	42	18	4	11	2	2	8	
31–40	42	16	1	4	1	1	6	
41–50	15	6	1	5	0	1	2	
51–60	6	1	0	2	0	0	1	
61–70	3	1	1	0	0	0	0	1
Totals...	198	92	12	51	10	6	39	3

* Total leucocyte and differential counts were done on only 100 of the 198 cases.

CAUSATIVE ALLERGENS IN PERENNIAL ALLERGIC RHINITIS

The substances considered to be the causative factors of the disease in this series are given in Table III. The outstanding point to be noted is the overwhelming incidence of the three common allergens, dust, feathers and orris root, and the paucity of cases, even in the first decade, associated with animal danders other than feathers. These three allergens, individually or in combination, account for 95 per cent of the series, and are spread over a wider range than the animal danders, which are restricted to the younger age group. The list of substances described in medical periodicals as capable of causing

allergic rhinitis is almost endless, and may tend to make our group of causative agents appear somewhat limited. This limitation is probably due to the fact that our series is composed entirely of private patients who rarely have contact with occupational factors such as grain dusts, chemicals, and irritating smoke or fumes.

Specific foods were not considered to be a cause in any of the cases. The opinion that food substances frequently cause allergic rhinitis has been strongly upheld by Rowe (6), Vaughan (5), Eyermann(7), Walker (2), and others, and although it is true that many of the patients in this series showed skin reactions to various foods, their importance as aetiologic agents in this series could not be demonstrated.

TABLE III

Causative allergens in 198 cases

AGE IN DECADES	CAUSATIVE ALLERGEN					
	Feathers	Dust	Orris	Animal danders	Kapok	Cottonseed
1–10	30	39	29	2	2	1
11–20	20	20	12	2	2	1
21–30	21	27	19	4	3	1
31–40	19	30	13	1		
41–50	8	10	5			
51–60	3	5	1			
61–70	2	2				
Totals.....	103	133	79	9	7	3

TREATMENT OF PERENNIAL ALLERGIC RHINITIS

Until recently our treatment of perennial allergic rhinitis has consisted of two procedures—avoidance of the offending allergen or allergens, and the subcutaneous injection of a potent extract of the same in gradually increasing doses. More recently, as stated in the introduction, ionization of the nasal mucosa has been employed, but none of the patients in this series was subjected to this procedure.[3] Multi-

[3] Preparation of extracts and treatment therewith was essentially as follows: the crude material was washed with ether until washings returned clear, then immersed in Coca's solution for 48 hours, and filtered through a Berkefeld filter. The filtrate represents the concentrated extract. Culture was always done to

ple injections of the indicated extracts were given to 137 of the 198 patients and, in addition, they were instructed to avoid contact with the corresponding allergens as far as possible. The results of treatment are summarized in Table IV. In 113 (82 per cent) of the patients there was a favorable response: 53 were considered definitely well and were free of symptoms; 55 were markedly improved; and 5 slightly improved, when treatment was discontinued or at the end of our observations, which extended for from one to ten years.

The actual duration of treatment by injection varied greatly; some received treatment for from one to two months, and others for as long as five years; others were given several courses dependent on the

TABLE IV

Results of treatment in 137 cases

AGE AT ONSET	NUMBER OF PATIENTS	DURATION OF SYMPTOMS	RELAPSES	WELL	IMPROVED GREATLY	IMPROVED SLIGHTLY	UNIMPROVED
		years					
1–10	35	7	17	19	9	2	5
11–20	21	10	15	6	9		6
21–30	27	5	15	9	12	2	4
31–40	40	4	17	14	18	1	7
41–50	8	5	5	2	3		3
51–60	4	2	1	1	2		1
61–70	2	2	2	2			
Totals.....	137	Average 5 years	81	53	55	5	26

recurrence of symptoms. Relapse or recurrence of symptoms following initial relief from treatment frequently occurred. In this series 60 patients experienced 81 relapses despite the continued avoidance of the allergens considered as the cause of symptoms. It appears,

determine sterility. Treatment was usually begun with 0.1 cc. of a 1–100 or 1–1000 dilution or higher if indicated, as in the case of highly potent antigens such as cottonseed and animal danders, and increased 0.1 cc. per dose, twice a week. When the 1–10 dilution was reached, the treatment interval was lengthened to 1 week; if and when symptoms improved or disappeared, treatment every two weeks for a variable period was continued. For details regarding preparation of extracts reference to the standard textbooks should be made.

therefore, that a tendency to relapse is characteristic of the disease. In this respect it is comparable to pollen hay-fever in which recurrence is the rule when treatment is interrupted.

Which of the two methods of treatment, namely, desensitization or avoidance of the causative allergens was the more important factor in bringing about improvement in 82 per cent of the 137 cases cannot be definitely answered, as a control group of patients untreated by desensitization is not available. Although 51 patients were not given specific injections, information concerning the majority of them could not be obtained because many of them disappeared from observation and could not be traced when this study was undertaken. The value of desensitization can be appraised, however, from that group of patients who suffered relapse when specific treatment by injection was stopped. As stated above, 60 or almost 50 per cent of the 137 patients treated by both methods suffered 81 relapses, and these relapses responded favorably to specific desensitization with the appropriate extracts. It can be stated, therefore, that in 60 of the 137 patients, this method appeared to be the more important form of therapy.

No relationship appeared to hold between the duration of symptoms and the eventual response to treatment. During the first two decades of life, symptoms had existed longer than during the later decades, yet the outcome of treatment is roughly equal in all age groups. Again, the age at which symptoms had begun did not apparently influence the prognosis. It was also impossible to predict with any degree of certainty the amount of treatment necessary for any individual case. Some improved rapidly after relatively few injections, while others failed to exhibit any response until stronger solutions were reached.

Failure to respond to treatment was observed in 24 cases (18 per cent). No satisfactory explanation for these failures is forthcoming. Several patients became discouraged early in the course of treatment, and inadequate therapy may have accounted for the poor results recorded in these cases. Failure to identify the specific substances inciting symptoms may have been responsible for other poor results. It is also possible that some of these patients lacked the capacity to respond to injections of antigens, since it is well known that a small percentage of pollen hay-fever cases in which specific hypersensitivity

has been definitely established fail to improve despite persistent injections of pollen extracts. Again, adherents to the opinion that specific foods cause allergic rhinitis may suggest that this factor played a rôle in these cases despite our failure to demonstrate such a relationship.

Some patients were given only one, and others a mixture of allergens. In table V a comparison between the results of treatment with single and multiple allergens is shown. Patients receiving single allergens, such as dust, orris root or feathers, responded about as well as the group treated with a mixture of two or three allergens; relapses were not more frequent, and the eventual outcome was essentially the same in all age groups. Because of the variable nature of house dust

TABLE V

Comparison treatment with single and multiple allergens

	SINGLE ALLERGENS			MULTIPLE ALLERGENS					
	Dust	Orris	Feathers	Feathers, dust	Dust, orris	Orris, feathers	Orris, feathers, dust	Dust, orris, kapok	Dust, orris, cottonseed
Number of cases	36	18	10	38	20	10	17	2	1
Improved or well	24	13	7	25	15	6	12	1	1
Relapses	14	7	1	11	9	3	8		
No improvement	7	3	2	9	2	2	4		
No data	5	2	1	4	3	2	1	1	

and the widespread sensitivity to it, it is significant to note that this substance was considered the most frequent cause of symptoms, and further, that treatment with its extract was as successful as with other extracts.

UPPER RESPIRATORY INFECTION IN PERENNIAL ALLERGIC RHINITIS

As stated in the introduction, we have excluded from this study patients presenting symptoms simulating those of perennial allergic rhinitis which proved to be due primarily to infection of the upper respiratory tract. Combinations of allergic rhinitis and infection, particularly of the paranasal sinuses or of the lymphoid tissue of the naso-pharynx, are not uncommon, and the importance of recognizing the former process has been emphasized by Grove and

Cooke (8), Balyeat (10) and by Hansel (11), who has recently reviewed the whole subject. Such a combination was observed in 22 instances in this series, as illustrated in Table VI. Of these, sinusitis was present in 11 and tonsillitis in 9 patients. On the basis of our observations, these infections were regarded as either secondary complicating factors arising as a result of allergic irritation, or of coexistent foci of infection unrelated to the manifestations of hypersensitivity. The striking symptoms of sinus infection simulating those of allergic rhinitis are nasal congestion or turgescence of the mucosa with varying degrees of obstruction, associated with a minimal rhinorrhea. On the other hand, one *rarely* encounters, in sinusitis, any itching or sneezing—symptoms so common in allergic rhinitis. Careful history-taking,

TABLE VI

Incidence of infection and operations

AGE IN DECADES	TONSILITIS	SINUSITIS	PRIOR OPERATION		OUR OPERATIONS
			Tonsils	Sinuses	
1–10	4	1	3	1	2
11–20	0	1	0	3	0
21–30	0	2	2	4	1
31–40	2	5	0	3	3
41–50	2	3	0	0	0
51–60	1	1	1	1	
Totals.....	9	13	6	12	9

which is most important in differentiating between these two forms, should not be neglected even in the face of marked skin reactions, which might be erroneously interpreted as the cause of symptoms in the infectious type.

Experiences frequently related by patients suffering from perennial allergic rhinitis are repeated operations, submucous resection or operations on the sinuses before specific hypersensitivity was discovered. In this series, 12 such patients failed to show permanent improvement until the appropriate desensitization therapy was instituted. Operative procedures, on the other hand, in some cases may be a necessary adjunct in successful treatment. A hyperplastic nasal mucosa with or without polyp formation and subsequent infection, usually of the

chronic form, not infrequently follows prolonged allergic irritation, and although desensitization may reduce the symptoms, complete relief is still not obtained. Corrective surgical measures should then be instituted, and in 9 cases in this series such steps were considered necessary. Again, the complicating infection may gradually subside coincidently with the prescribed treatment, and in 11 instances this sequence was observed. It is usually wise, if possible, to determine the effect of desensitization before specific surgical steps are undertaken.

SUMMARY

In this paper 198 cases of perennial allergic rhinitis are presented. This diagnosis should be restricted to patients suffering from perennial nasal symptoms for which a definite allergic basis is demonstrated.

In a higher percentage of cases the onset of symptoms occurred during the first decade of life; thereafter, the incidence is roughly uniform through the third decade, but then diminishes rapidly. Males outnumbered the females during the first decade; thereafter the reverse was true.

A positive family history was obtained in 50 per cent. Only 12 per cent of 100 patients had eosinophilia. Other allergic manifestations observed were the following: asthma in 25 per cent; pollen hayfever in 20 per cent; eczema, urticaria and food sensitivity each in less than 5 per cent. Of the entire group, in 50 per cent they appeared during the first decade of life.

House dusts, feathers, and orris root either singly or in combination, were considered as causing the disease in 95 per cent of the patients; animal danders (other than feathers), kapok and cottonseed in the remaining 5 per cent. Foods were not thought to be significant in any of these cases.

Treatment simultaneously by avoiding the causative allergens as far as possible, and by the parenteral injection of potent extracts of the same was successful: 82 per cent of 137 patients in this way were either definitely improved or well (53 patients were well; 55 were markedly improved; 10 were 50 per cent improved, and 5 were slightly improved) when treatment was stopped, or for from one to ten years thereafter. Causes of failure in the other 18 per cent could not be determined. Relapses occurred after cessation of treatment 81 times

in 60 patients, and in this group, desensitization appeared to be the more important form of therapy. No relationship between the duration of symptoms or age at onset and response to treatment was noted. No fixed period of treatment can be predicted for any given case, as some patients improved quickly after a few injections of antigen, whereas others did not respond until higher doses of the appropriate extracts were reached.

In 22 instances infections of the paranasal sinuses or of the lymphoid tissue of the naso-pharynx were found. These infections were considered as secondary complicating factors, or as coexistent foci unrelated to the rhinitis. In 9 cases operative procedures were considered as necessary supplementary steps to relieve symptoms; in 11 instances the infections subsided coincidently with treatment by desensitization.

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DECORTICATE POLYPNEIC PANTING IN THE CAT

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Investigations dealing directly with the neurological mechanisms concerned in the regulation and control of respiration have been extensively reported in the modern literature. Further observations have also been made indirectly in the course of experiments undertaken for other purposes. Several observers (Bard, 1928; Bard and Rioch, 1937) noted that decorticate cats often exhibit a polypneic type of respiration either spontaneously or in response to mild grades of hyperpyrexia. Although polypneic panting is an uncommon form of respiration in the cat at usual temperatures, it is, nevertheless, observed when the normal cat is exposed to a sufficiently warm environment. This respiratory response to raised temperature is readily identified and is the same behavior exhibited so commonly by dogs. The polypneic panting which follows decortication and which does not require a raised body or environmental temperature is of precisely the same type. Its peculiar characteristics are (Otenasek and Lilienthal, 1936):

(a) The respiratory rate is extremely rapid, varying in the majority of instances between 100 and 300 a minute.

(b) Rhythmicity of respiration may be maintained uninterruptedly at these accelerated rates for periods as long as one and one-half hours. In contrast to the usual relationship, the inspiratory and expiratory phases become equal in duration.

(c) The volume of tidal air is reduced. This may be noted readily in the obvious limitation of the amplitude of movement of the thoracic cage, and in the reduced excursion of the recording tambour. The impression is gained that breathing is effected with a partially expanded chest, for the thorax does not collapse during expiration

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to the extent seen in conditions requiring augmented pulmonary ventilation, such as excessive hemorrhage or anoxemia. The overventilation is apparently confined to the dead space.

(d) The mouth is held open, the labial commissures are retracted rhythmically, and the tongue is moved to and fro upon the floor of the mouth synchronously with respiration. At extreme elevations of rate, these rhythmic accompanying movements spread to the pharynx, larynx and nares.

In the determination of the inception of polypneic panting we have taken the presence of the tongue movements in the open mouth as a readily observed criterion; thus, in arbitrary fashion, we have chosen the appearance of this phenomenon as a signal of the onset of polypneic panting.

Bard (1928) in a study of sham rage noted that polypneic panting occurred in some of the preparations but not in others. Since the animals had been deprived not only of cortex but also of additional portions of the forebrain this suggested the possibility that sham rage and polypneic panting are separable phenomena.

The present series of experiments was undertaken to determine, if possible, the nature of decorticate polypneic panting, and to delimit anatomically, in acute preparations, the region of the brain stem necessary for the production of this excessive respiratory activity.

METHODS

All operations were carried out on adult male cats (with two exceptions) under insufflation ether anesthesia maintained by an ether cone until cannulation of the trachea permitted easy use of an ether bottle. The common carotid arteries were ligated in the neck, and the animal was placed in the prone position.

At the outset of this investigation, it was determined empirically that the successful outcome of an experiment was dependent primarily upon the rapidity with which operative maneuvers were executed. Consequently, once the cranium was opened, decortication and subsequent brain stem transection were performed without any rigorous attempt to maintain absolute hemostasis during the two or three minutes required for these operative procedures. In none of the cases reported did severe persistent hemorrhage occur from the skull or the brain.

The method of operative approach was essentially that described by Bard (1928). In the earlier experiments decortication was performed by means of a small, moderately sharp, L-shaped instrument which was placed behind and under the occipital lobes and drawn obliquely forward until the entire cortex had been

separated from the brain stem. Second stage transections were then made at various levels of the brain stem by means of a sharp spatula. In the later operations, in which it was desired to preserve only the various parts of the posterior diencephalon as the most rostral level of the remaining brain stem, an incision was made with a sharp scalpel into, and parallel with, the suprasylvian gyrus, down into the lateral ventricle. The hippocampus was thus exposed. A flat, narrow spatula was then used to dissect away the adjacent parts of the hemisphere. In this manner, the occipital poles were freed and amputated, thus exposing the corpora quadrigemina, the epiphysis, and the caudal portion of the dorsal thalamus for section at the desired level. With this technique the hemispheres, and all parts of the brain stem which were to be excised, could be removed in one stage.

Following section at the desired level, anesthesia was discontinued, and permanent hemostasis established. All brain tissue rostral to the point of transection was then completely removed from the cranial cavity and a careful inspection made to verify the level of the section. The cavity was then loosely packed with small cotton sponges, and the wound closed.

Experience has shown that in any one animal it is more practical to make single transections than successive ones. For this reason we have, in general, completed all operative maneuvers at one time and as briefly as was compatible with accurate ablation and rigid, final hemostasis.

Respiratory movements were recorded by means of a pneumograph consisting of an inflated rubber belt fastened about the lower thorax of the animal and attached to a Marey tambour. Blood pressure tracings were secured by means of a recording mercury manometer connected with a femoral artery. The body temperature of the cats was determined by inserting a thermometer into the rectum to a depth of 7 to 9 cm.

Following the cerebral ablation each animal was studied for periods of from one to four hours. In some cases the body temperature was maintained at the normal level throughout the experiment; in others the influence of lowering and raising the temperature was studied. Heating was achieved by means of an electric pad closely applied to the cat. When it was desired to lower the temperature of the animal a cold water bath was used.

At the end of an observation the animal was immediately killed, the brain carefully removed and preserved in 10 per cent formalin. The level of section was determined on the gross specimen.

PHYSIOLOGICAL OBSERVATIONS

The results of 32 successful experiments serve as the basis of this report. Other experiments are not considered because the animals deteriorated rapidly.

A. *Decorticate polypneic panting at normal body temperature.* In a large proportion of cats, ablation of the cerebral cortex with immediate

discontinuance of the ether anesthesia was followed within a brief but variable period of time by the onset of polypneic panting. In every such preparation, from the beginning of the experiment to the onset of polypneic panting, rectal temperature never varied more than 0.5°C. from 37.5°C. which is about 0.7°C. below the average normal level. This temperature was maintained until efforts were made to raise or lower it by artificial means. When the ether anesthesia was moderately light the respiratory rate of intact cats used in our experiments varied between 20 and 30 a minute. After the discontinuance of anesthesia, when the operative maneuvers were completed, this slow rate continued for a variable period of time.

In one group of 8 experiments the polypneic panting began within 10 minutes of the extirpation of the cerebral cortices and withdrawal of anesthesia. The appearance of panting in these animals was characterized by its abruptness. For example, in one instance the respiratory rate rose from 25 to 150 within the space of 1 minute, and in the following 9 minutes the rate attained 260, a tenfold increase. As the rate rose above 100 a minute, the familiar characteristics of polypneic panting became evident: decreased amplitude of the thoracic excursion, open mouth, rhythmic retraction of the labial commissures, and accompanying tongue movements. An abstract of the protocol of such an experiment follows.

Cat 5. At 2:45 the cortices of both hemispheres were removed. No further sections were made. At 2:50 typical polypneic panting developed. The rate was 150 a minute. Rectal temperature at this time was 37.6°C. The respiratory rate rapidly increased, reaching a maximum of 260 a minute in ten minutes (3:00). No signs of sham rage appeared until 3:10, when fits of intense struggle, protrusion of claws, retraction of nictitating membranes, dilatation of pupils, and snarling movements of the mouth first occurred. At this point the temperature began to fall gradually and reached a level of 36.8°C. at 3:25. This diminution of body temperature was accompanied by a slowing of respiratory rate, which reached a minimum of 100 a minute at this time. At 3:52 the animal became quiet and the experiment was terminated.

In a second group of experiments, the onset of polypneic panting was a more gradual process. Over a period of 20 to 30 minutes, and in one case of 50 minutes, the respiratory rate rose by small increments until the complete manifestations of polypneic panting had appeared. An abstract of the protocol of such a preparation follows.

Cat 10. Ether was begun at 1:47 and the cortices of both hemispheres had been extirpated by 2:20. In 15 minutes the first signs of rage appeared. The rectal temperature was 37.5°C. at this time, and did not fall below 36.5°C. for the duration of the experiment. Following decortication, the respiratory rate rose from 60 a minute at 2:20 to a maximum of 200 a minute at 3:00, when all the characteristics of polypneic panting were observed. Signs of pseudaffective activity appeared at varying intervals. At 3:25 a second section of the brain stem was made through the thalamus. This transection ran from a point 7 mm. rostral to the epiphysis to a level 3 mm. anterior to the optic chiasm. The sectioning was accompanied by a brisk hemorrhage. Respirations slowed somewhat (100 a minute) but retained all the characteristics of polypneic panting. Ten minutes later, at 3:35, the blood pressure fell to a critical level, the temperature fell to 34.5°C. and the animal was sacrificed.

It may be stressed here that the appearance of polypneic panting in these decorticate animals was neither dependent upon nor a result of any appreciable alteration in either the environmental or body temperature of the animal. The panting occurred at body temperatures ranging from 37.0° to 38.0°C.; and the room temperature remained within 1.0°C. of the initial level, which varied on different days from 21.0° to 24.0°C.

B. *Alterations in polypneic rate with variations in body temperature.* Decorticate polypneic panting, when once established under constant experimental conditions, is a relatively stable phenomenon. However, the induction of changes in the body temperature of decorticate preparations exhibiting polypneic panting results in obvious modifications in respiratory rate. Although the modifications are in no wise directly proportional to the changes in body temperature, they are, nevertheless, in the same direction. Thus, cooling a decorticate preparation, which is panting in typical polypneic fashion, results most frequently in a sharp drop in respiratory rate, although the other characteristics of polypneic panting remain unchanged (diminished thoracic excursion, open mouth, retracted labial commissures, and to and fro tongue movements) (fig. 1). Subsequent elevation of rectal temperature produces a return to the prior high rate. At an elevated temperature the respiratory rate is usually not proportional to the rise in body temperature; it merely changes in the same direction. Thus, the respiratory rate varies roughly with variations in body temperature. The abstracted protocol of a preparation which exhibited such variations follows.

FIG. 1

FIG. 2

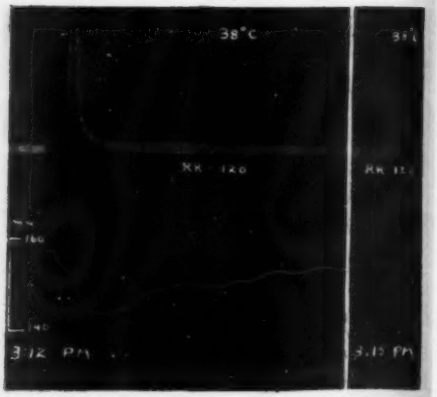


FIG. 3

FIG. 4

FIGS. 1–4

Cat 22. Decortication at 2:19. The cat began to pant almost at once at 240 a minute with rectal temperature 38.0°C. at 2:23. A maximum of 280 a minute was recorded at 2:30 when cooling was begun. The cat displayed sham rage at short intervals. At 2:50 when a rectal temperature of 34.5°C. was recorded, the rate had fallen to 84. All signs of polypneic panting persisted, however. Heat was now applied and continued until the rectal temperature reached a maximum of 40.0°C. at 3:47 when the respiratory rate was 280 a minute. Cooling was begun once more but the intense fits of sham rage were accompanied by a gradual fall in blood pressure so that the experiment was terminated at 4:18.

The continuance of polypneic panting in the face of a lowered body temperature was not, however, a constant finding. After more extensive ablations than simple decortication lowering of body temperature resulted in a more rapid depression of respiratory rate and an earlier disappearance of polypneic panting. This, however, was a reversible phenomenon, for the complete polypneic pattern reappeared when the cooled animal was warmed to a normal or supranormal temperature.

C. *Polypneic panting does not occur in the hypothalamic preparation.* It is a well-established fact that decerebrate cats (transection of the brain stem at the intercollicular level) do not exhibit polypneic panting (Bazett and Penfield, 1922; de Almeida and Xavier, 1930; Bazett, 1932; Bazett, Alpers and Erb, 1933). We have been at some pains to determine, as precisely as is possible with this particular experi-

FIG. 1. CAT 22. DECORTICATE. THE EFFECT OF CHANGES OF BODY TEMPERATURE UPON THE RATE OF POLYPNEIC PANTING

Upper tracing: respiration. Lower tracing: time in seconds.

FIG. 2. CAT 18. THE EFFECT OF ABLATION OF THE DORSO-CAUDAL DIENCEPHALON UPON DECORTICATE POLYPNEIC PANTING

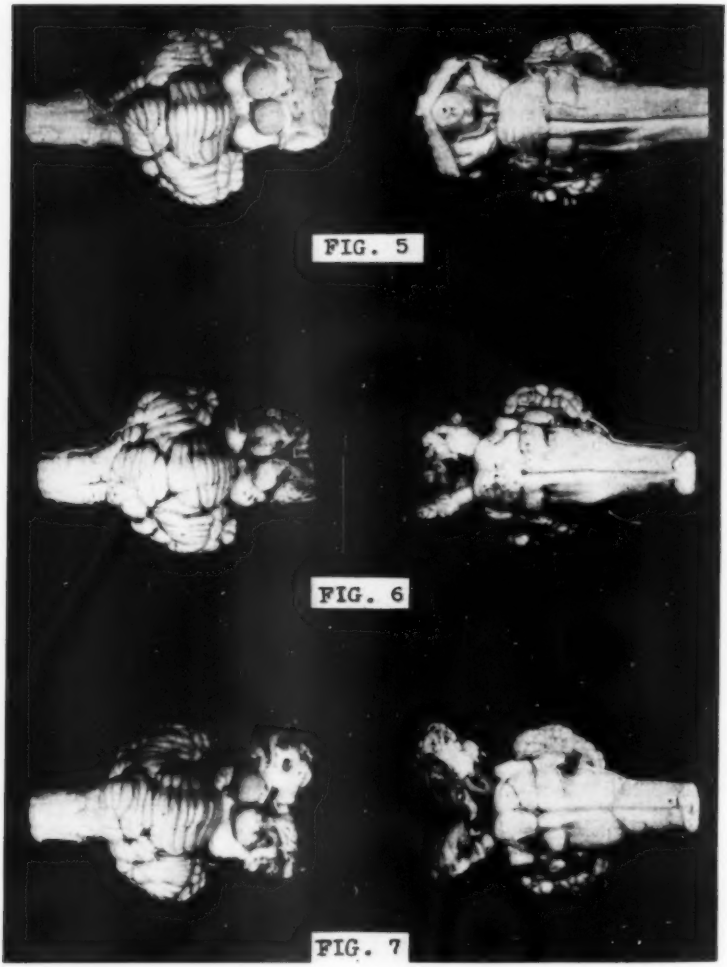
Removal of this area at 2:30 resulted in immediate cessation of polypneic panting. Tracings as in figure 1.

FIG. 3. CAT 26. DECORTICATE. THE PHYSIOLOGICAL DISSOCIATION OF POLYPNEIC PANTING AND SHAM RAGE

The period of spontaneous sham rage indicated by the abrupt rise in blood pressure and variations in respiration as described in the text. Upper tracing: respiration. Middle tracing: blood pressure. Lower tracing: time in seconds.

FIG. 4. CAT 11. CORTICES AND ANTERIOR HALF OF THE DIENCEPHALON ABLATED

Rhythmic manifestations of sham rage with the maintenance of polypneic panting in the quiet intervals. Tracings as in figure 3.



FIGS. 5-7

mental approach, the most caudal complete transection of the brain stem which does not interfere with the capacity for decorticate polypneic panting.

In the first group (A) of 9 acute experiments, the dorsal level of the final transection began precisely at the rostral border of the superior colliculi and extended ventrally through the hypothalamus to the optic chiasm (fig. 5). In this type of preparation spontaneous polypneic panting at normal post-anesthetic temperature (37.5°C. ±0.5°) did not occur. In an attempt to induce polypneic panting these animals were heated, in one case to a maximum of 42.0°C., but no signs of the polypneic response were detected during the course of the experiments, which ranged in duration up to three hours. These "hypothalamic" preparations had lost the capacity to pant in the polypneic fashion. A protocol abstract of such an experiment follows.

Cat 13. At 1:58 anesthesia was begun, and decortication was completed at 2:27. Five minutes later (2:32) a "hypothalamic" section was made, running from the superior colliculi to the optic chiasm. Temperature 37.5°C., and respiratory rate 42 a minute. At 2:58 the first mild signs of sham rage appeared. Subsequently there were terrific outbursts of rage at very frequent intervals—intense struggle, tail waving, sweating, dilatation of pupils, snarling, etc. Respiratory rate rose slowly from 60 to 110 a minute, but none of the characteristics of polypneic panting were observed. Temperature and pseudaffective activity remained unchanged during the course of the experiment. Polypneic panting never appeared. Sacrificed at 4:00.

The rise in respiratory rate in these preparations, which did not exhibit polypneic panting, is part of a respiratory phenomenon termed *hyperpneic* panting and will receive further attention below.

FIG. 5. CAT 13. PHOTOGRAPHS OF DORSAL AND CAUDAL ASPECTS OF REMAINING BRAIN STEM

Plane of transection: Rostral border of superior colliculi to optic chiasm. This animal exhibited sham rage but no polypneic panting.

FIG. 6. CAT 26

Plane of transection: 3 to 4 mm. rostral to superior colliculi to rostral border of infundibulum. This animal exhibited both sham rage and polypneic panting.

FIG. 7. CAT 30

Plane of transection: 3 to 4 mm. rostral to superior colliculi to caudal border of mamillary bodies. This animal exhibited no pseudaffective activity but panted vigorously.

D. *Polypneic panting follows sections which leave intact the caudodorsal portion of the diencephalon.* In a second group (B) of 9 acute experiments the level of transection of the brain stem differed from that in group A. Here, the dorsal level of the transection began 3–4 mm. rostral to the superior colliculi and descended along various planes to strike the base in the general hypothalamic region, *i.e.*, between the optic chiasm and the anterior border of the mamillary bodies (fig. 6). The animals of this group retained the capacity for polypneic panting. The phenomenon, when it appeared, was similar in every particular to that which in other preparations followed simple decortication. However, the inception of polypneic panting in this group of cats, from which a large portion of the diencephalon had been ablated, was not so abrupt a process. In some of these cases, polypneic panting did not appear spontaneously at normal body temperatures but required an elevation of temperature to initiate it. The appearance of polypneic panting without the stimulus of an elevated body temperature is exemplified in the following protocol.

Cat 26. Decortication and hemostasis were complete at 2:27. Temperature throughout the experiment ranged between 37.5° and 38.2°C. Neither heat nor cold was applied at any time. Typical polypneic panting set in at 2:57 and continued thereafter at rates ranging from 100 to 140 a minute. There were signs of mild pseudaffective activity. At 3:45 ether was again administered to control the outbursts of sham rage and a transection was made. It extended from a point 3.5 mm. rostral to the epiphysis to the anterior border of the infundibulum. Polypneic panting and rage were resumed 10 minutes after this transection and continued for the duration of the experiment at rates varying from 130 to 170 a minute. All associated phenomena were present. Temperature remained constant at 37.5°C. The experiment was terminated at 4:00.

The protocols of Cats 29 and 30, both members of this group, will be found below.

In the case of Cat 26 the second ablation, which left intact the caudal portion of the diencephalon, did not abolish the capacity for decorticate polypneic panting. In striking contrast to this result was an experiment in which the secondary transection, ablating the caudodorsal portion of the diencephalon, put an end to the polypnea, but did not interfere with the display of sham rage. The protocol follows.

Cat 18. At 2:15 decortication was complete. Typical polypneic panting began at once with a rate of 180 a minute at a rectal temperature of 37.5°C. For

the next 11 minutes the respiratory rate varied between 180 and 220 a minute. A clean transection was made across the brain stem in the mid-thalamic region at 2:26. The cat continued to pant after this procedure at a rate of 220 a minute and the temperature remained constant. At 2:30 the second transection was made. It passed from the epiphysis to the optic chiasm. Respiratory rate fell very abruptly (Fig. 2) to 30 a minute. Following this, the animal was placed in the dorsal position and immediately exhibited widespread signs of pseudaffective activity, but never panted. For the next 30 minutes the cat was heated reaching a maximum rectal temperature of 40.5°C., at 3:16. The respiratory rate rose slowly during this period from 30 to 50 a minute, but polypnea did not ensue. At 3:16 the blood pressure fell suddenly to a critical level and the preparation was sacrificed.

Preparations which form a transitional group between groups A and B will be described under section F.

E. *The relation of polypneic panting to sham rage.* In the majority of our animals which retained that area within the ventral and caudal portion of the diencephalon delimited by Bard (1928) as essential for the manifestation of sham rage (Cannon and Britton, 1925) that phenomenon developed. Its character may be recorded by a quotation from Bard's original description: "The pseudaffective phenomena . . . included struggling, attended by movements of the head and arching of the trunk with thrusting and pulling of the limbs; clawing movements of the forelegs with protrusion of the claws; waving and lashing of the tail; a snarling expression; *and very rapid panting with mouth open and movements of the tongue to and fro.* In addition to these activities were signs denoting a vigorous sympathetic discharge: . . . *These activities sometimes appeared in incomplete combinations, two or three of them being absent during the whole or a part of an experiment.*" (Italics ours.)

Although in the decorticate or "hypothalamic" cat exhibiting spontaneous, rhythmic outbursts of sham rage, panting is frequently observed, it is not, however, an integral and inseparable manifestation. Rather is the association of polypneic panting with quasi-rage dependent upon the plane of the brain-stem transection employed to produce the preparation.

In those 7 of our experiments in which the dorsal level of transection was at the rostral border of the superior colliculi and the ventral level at the optic chiasm, the cats exhibited the entire group of pseud-

affective activities, but polypneic panting neither appeared spontaneously nor could it be elicited by heating the animal (fig. 5). Hyperpneic panting, which is to be described below, was the sole respiratory response to the elevation of body temperature. Protocols of such preparations (Cats 13 and 18) have been given above. Even in these animals whose capacity for polypneic panting had been abolished, there did occur, during the period of quasi-rage and its concomitant somatic struggle, an advance in respiratory rate, but the type of respiration differed very definitely from that of true polypneic panting. With the activities heralding the onset of the pseudaffective fit the animal inspired deeply, the thorax was fixed in partial expansion, and respiration consisted of many short, arrhythmic gasps, culminating in a sighing expiration at the close of the period of activity. Then the former even rate was resumed (figs. 3 and 4). That these modifications of respiration do not result from the abrupt rise in blood pressure attendant upon the outburst of sham rage is amply demonstrated by the following observations. First, the change occasionally precedes the rise in blood pressure (fig. 4). Second, we have sometimes observed sudden rises in blood pressure which were not accompanied by the usual alterations in respiration. And finally, Cat 15, which was a pregnant female, exhibited the familiar respiratory change with each bout of sham rage, but failed to show any change whatsoever in blood pressure throughout the course of the experiment. This anomalous observation was confirmed in a second similar experiment upon another pregnant female (Cat 14). Further evidence of the physiological separation of polypneic panting from sham rage is furnished by the observation that occasionally in those preparations retaining the caudal portion of the diencephalon sham rage appeared without demonstrable alterations in the respiratory rate or rhythm, although further observation proved that the capacity for polypneic panting had been retained.

By means of transections in suitable planes we have been able to demonstrate the anatomical dissociation of the central controlling mechanisms of polypneic panting and quasi-rage. This dissociation was established in experiments in which a state, the converse of the one just described, was obtained; *viz.*, retention of the capacity to show spontaneous polypneic panting at normal body temperatures

(or at an elevated body temperature) with complete absence of any pseudaffective activity. This condition was obtained by a transection the plane of which extended from a dorsal point 3–4 mm. rostral to the epiphysis to a ventral level which coincided with the caudal border or the middle of the mamillary bodies (fig. 7). This type of preparation, as shown in the protocol abstracts which follow, exhibited polypneic panting, but evidence of sham rage was never observed; the animals remained quiescent through the experiment. In contrast to the cats which showed sham rage but failed to pant, the four animals of this group retained a small portion of the caudo-dorsal thalamus, an area which lies below the habenular complex and surrounds the anterior part of the iter. In them, however, the entire hypothalamus was extirpated. The only perceptible signs of sympathetic activity in these preparations were slow waves in blood pressure, which were unaccompanied by any evidence of pseudaffective activity. This same vasomotor phenomenon is frequently observed in animals with even more caudally placed transections; and, when appearing alone, is not a manifestation of sham rage.

That the absence of pseudaffective activity in these experiments cannot be attributed to trauma is indicated by Bard's (1928) numerous observations that transections at this level, separating the caudoventral portion of the diencephalon from the mesencephalon, invariably abolished the capacity to develop sham rage. The plane of transection which we employed in this group of experiments deprived the animals of this very portion of the diencephalon. The protocol abstracts of two examples of this group of experiments follow.

Cat 29. At 2:35 the occipital poles were amputated. The exposure thus effected permitted the immediate transection of the brain stem from a point 3 mm. rostral to the epiphysis to the rostral border of the mamillary bodies. Throughout the experiment the temperature varied between 37.0°C. and 38.0°C. Neither heat nor cold was applied. At 2:40 the respiratory rate was 30 a minute. It continued slowly to rise until at 3:05 the rate was 85 a minute. Tongue movements and all the associated phenomena of polypneic panting appeared as the rate increased. At 3:15 polypneic panting was in full course with a respiratory rate of 100 a minute. At this time the cannula was inadvertently torn from the femoral artery. There occurred a brisk, uncontrollable hemorrhage and the animal was sacrificed.

Cat 30. At 2:25 the occipital poles were retracted and a transection of the

brain stem made from a point 3 mm. rostral to the epiphysis to the posterior borders of the mammillary bodies. Temperature throughout the experiment varied between 37.2°C. and 37.8°C. At 3:05 the animal was breathing deeply at 40 a minute. At 3:25, twenty minutes later, tongue movements were observed for the first time as the mouth was passively opened; respiratory rate was 110 a minute. At 3:30, the mouth was opened spontaneously and polypneic panting at a rate of 160 a minute began. Slight gradual changes in blood pressure occurred but no evidence of generally increased sympathetic activity was detected. The animal remained entirely quiet. At 3:50 respiration had continued unchanged. At 4:00 a gasping respiration started suddenly, blood pressure began a steady fall, and the experiment was terminated. Panting had been steady, starting approximately one hour after transection of the brain stem and continuing without interruption for the duration of the experiment. No signs of sham rage appeared at any time.

In two experiments transections were performed in order to eliminate all areas within the neuraxis thought to be requisite for the expression of rage and for polypneic panting. Here, the transection began dorsally between the superior and inferior colliculi and extended ventrally to strike the base 3–4 mm. caudal to the roots of the oculomotor nerves. In these animals no polypneic panting appeared spontaneously, nor could it be induced by elevation of the body temperature. Furthermore, the animal remained totally inactive throughout the course of the experiment. Slowly rising and falling waves of blood pressure were observed in one experiment. Heating produced a moderate rise in respiratory rate accompanied by a hyperpnea which is to be described below under section F.

F. *Hyperneic breathing.* Observations by Bazett and Penfield (1922), Sherrington (1924), Bazett (1932), and Bazett, Alpers and Erb (1933) have established the fact that in the cat transections of the brain stem which extirpate cerebral structures lying anterior to a plane extending from the superior colliculi to the optic chiasm abolish the polypneic response to elevation of the body temperature. With a rise in body temperature of such cats there did occur in our series, however, a moderate elevation in the respiratory rate, a type of response best designated *hyperpneic breathing* (Pinkston, Bard and Rioch, 1935). This hyperpneic breathing differs from polypneic panting in unmistakable fashion. In the former the respiratory rate rarely rises above 80 to 100 a minute, the mouth is closed, the tongue does not execute to and fro movements, and the amplitude of the

thoracic excursion (*i.e.*, the volume of tidal air) is markedly augmented. This increase in respiratory amplitude is recognizable at a glance; it resembles in all particulars the type of labored breathing produced by raising the alveolar carbon dioxide tension.

Within this group of experiments, where hyperpnea but not polypneic panting occurred there was one preparation whose abstracted protocol appears below.

Cat 20. At 2:14 removal of all cerebral cortical tissue was completed. At 2:20 a clean transection passing from the epiphysis to the optic chiasm was made. At 2:30 rectal temperature was 36.0°C. and the respiratory rate 30 a minute. At 2:49 the first manifestations of sham rage were evident and heating was begun. The respiratory rate rose to a maximum of 160 a minute at 2:59 when rectal temperature was 40.0°C. The rate remained relatively elevated (130 to 160 a minute) during the continued application of heat, but the other characteristics of polypneic panting were never observed. The animal continued to show sham rage until 3:25, when gasping respiration set in, and shortly thereafter the experiment was terminated.

This animal exhibited a form of respiration which obviously is transitional between the complete polypneic phenomenon seen in the decorticate cat and the hyperpnea evocable in the midbrain preparation. The elevated rate (160 a minute) was the sole manifestation of the polypneic pattern. The plane of section, which in this particular animal seemed to be identical grossly with that which in all similar preparations abolished polypneic panting, may have removed but a portion of the neural structures requisite for polypneic panting.

DISCUSSION

The absolute similarity of decorticate polypneic panting and the polypnea shown by the normal animal in response to heat suggests that the two phenomena may be elaborated by a common central mechanism. It is even possible that decorticate panting, which is not dependent on any change in body or environmental temperature, is the result of some functional alteration in the central neural machinery essential for thermal panting. At any rate certain experimental facts derived from studies of temperature control are quite relevant to any discussion of our observations.

The central neural mechanisms concerned in the homeostasis of

body temperature have been the subject of much investigation. The rôle played by the forebrain has been examined recently by Pinkston, Bard and Rioch (1935), and they have outlined the earlier contributions to this complex problem. Bucy and Case (1936) have published data concerning their observations on the regulation of respiratory rate by the cerebral cortex and have reviewed the pertinent literature. The work of Bazett, Alpers and Erb (1933) has a more direct bearing upon the experiments whch we have reported above. The evidence which they adduce, together with the observations of several earlier investigators, indicates that the hypothalamus plays a prepotent rôle in the integration of thermoregulatory responses. These observers examined surviving cats from which had been extirpated all cerebral structures lying rostral to a plane extending from the caudal border of the superior colliculi to the optic chiasm. Their studies indicate that, while such preparations retain adequate responses to a cold environment, they are partially deficient in combating a rise in body temperature. They noted aberrations from the normal pattern of response which included lack of sweating of the foot pads and absence of polypneic panting in the face of an elevated body temperature.

That the capacity to show polypneic panting in response to thermal stimulation fails after separation of the diencephalon from the mesencephalon has been amply demonstrated (Bazett and Penfield, 1922; Sherrington, 1924; de Almeida and Xavier, 1930; Bazett, 1932; Hammouda, 1933). The conclusion which, perforce, must be drawn is that the central mechanisms essential for thermal polypneic panting lie rostral to the mesencephalon.

The sole evidence, of which we are aware, indicating that, in the cat, structures sufficient to mediate thermal polypneic panting may lie caudal to the diencephalon has been advanced by Keller. In a series of acute experiments (1929) in which he placed, *seriatim*, many transverse lesions in the pontile region, polypnea was abolished only when the sections included the extreme lateral portions of the pons. However, because of his finding, through inadvertent operative damage to the inferior colliculus, that polypnea might be abolished by slight damage to areas which he believes are not concerned in the polypneic mechanism, he states that "if a lesion interferes with polypnea, it is not conclusive proof that the lesion has destroyed any tracts or centers

concerned with the polypnea mechanism." Again he states (1931) that ". . . rapid breathing is still possible after complete stem section below the cephalic pons level" as evidenced by his experiment 65. Unfortunately, Keller does not offer any conclusive evidence to support his inference that the transection in this experiment was complete. Finally, he has reported (1930) a "chronic midbrain animal" which exhibited typical panting. However, in all such experiments one is faced with the difficulty of deciding whether the transections were anatomically complete. An experiment wherein the nervous tissue lying rostral to a transection remains *in situ* possesses an inherent hazard; it is extremely difficult to insure complete transection unless the separated tissues are removed. No matter how skillful the operator, the type of procedure which Keller employed makes hazardous the claim that section was complete; the uneven surface of the floor of the skull requires the most complete exposure to verify and insure a total transection. We are, therefore, at a loss to offer any explanation of the results which Keller has reported and which, so far as we are aware, have not been confirmed. However, even if his contentions are correct, the many results mentioned above show that a prepotent polypneic mechanism is situated above the mesencephalon.

There is, in addition, a considerable body of evidence demonstrating that the central structures essential for thermal polypneic panting do not lie within the neopallium, rhinencephalon or striatum. In dogs deprived of these structures Pinkston, Bard and Rioch (1935) found that polypneic panting may occur only during a short postoperative period. It is at this time that the secondary thalamic degeneration, which inevitably follows removal of the neopallium, begins. After it has developed, the decorticate dog no longer exhibits polypnea in response to warming, and it seems highly probable that this deficiency is associated with the thalamic defect. Various acute experiments have indicated that in the dog the thalamic region is essentially involved in this particular thermal response. Thus Hammouda (1933) demonstrated thermal panting in decorticate dogs, but he found this could be abolished by "localized injuries to the thalamus." In the case of the cat the evidence is clear that decortication does not significantly modify the capacity to pant normally in response to thermal stimuli. Bard and Rioch (1937) observed that at sufficiently high

environmental temperatures their chronically decorticate cats, like normal cats, engaged in true panting. The difference between decorticate cats and dogs in the chronic state may mean that the essential central mechanism involved in thermal polypneic panting has a different localization in the two species. Another possible explanation is that in both animals the mechanism has the same locus, but is affected by secondary degeneration only in the dog.

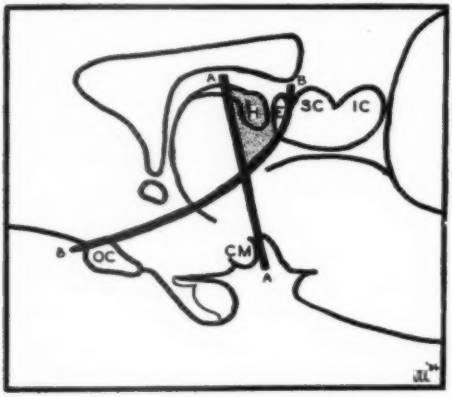


FIG. 8. SCHEMA OF SAGITTAL SECTION OF CAT'S BRAIN

Dotted area in the caudo-dorsal diencephalon is that region found essential for decorticate polypneic panting. Heavy lines indicate planes of crucial transections. *A–A*, eliminates hypothalamus and sham rage; *B–B*, eliminates caudo-dorsal thalamus and decorticate polypneic panting; *CM*, mamillary bodies; *E*, epiphysis; *H*, habenular complex; *IC*, inferior colliculus; *OC*, optic chiasm; *SC*, superior colliculus.

In his study of the quasi-rage of acutely prepared cats, wherein all structures rostral to the caudal one-fourth of the diencephalon had been ablated, Bard (1928) noted typical polypneic panting (see his experiments 5, 13, 26 and 33). We have confirmed the fact that such preparations retain the capacity for this activity (cats 5, 10, 11, 16, 18 and 22). But more important is our evidence that the "center" for decorticate polypneic panting lies within the caudo-dorsal portion of the diencephalon and is both anatomically and functionally

separable from the hypothalamic mechanism concerned in the elaboration of quasi-rage. This is clearly demonstrated by those of our experiments (cats 29, 30, 38 and 40) in which the level of transection extended caudally and ventrally from a point 3–4 mm. rostral to the anterior border of the superior colliculi to strike the base at the caudal border of the mamillary bodies. Figures 7 and 8 show how in these experiments the caudo-ventral portion of the diencephalon, essential for sham rage, had been ablated. In them, all that remained of the diencephalon was the area surrounding the habenular complex, the tissue enclosing the anterior mouth of the iter and the caudo-dorsal extent of the third ventricle. This type of preparation exhibited polypneic panting but no pseudaffective activity. Thus, the neural centers or connections requisite for decorticate polypneic panting in the cat must lie within this relatively circumscribed caudo-dorsal part of the diencephalon.

Substantiation of this conclusion is offered by the work of Bazett, Alpers and Erb (1933) to which reference has already been made. Their sub-chronic preparations, which retained only the hypothalamus and the anterior floor of the third ventricle as the rostral boundary of the remaining brain stem, possessed a relatively effective mechanism for the maintenance of constant body temperature. However, in the face of a rising environmental temperature, the mechanisms ordinarily employed to combat hyperthermia were deficient in some respects. Especially obvious was the absence of polypneic panting. These animals had been deprived of the caudo-dorsal part of the diencephalon, including the area which we have demonstrated to be essential for decorticate polypneic panting.

Graham Brown (1915) has presented evidence which supports our contention that this caudo-dorsal thalamic area contains an integral factor for the polypneic mechanism. In an acute animal under a "chemical narcotic" anesthesia, he transected the brain stem of an adult chimpanzee thus: "On the dorsal surface of the neuraxis it [the plane of section] passed about 3 mm. in front of (oral to) the anterior boundary of the anterior colliculi. The plane then passed somewhat backwards so that its ventral part cut through the midbrain at the level of the centre of the anterior colliculi. Thus the plane of section passed through the optic thalamus above and through

the midbrain below—the upper third of the surface being composed of thalamus." The thalamic structures which were thus preserved made a preparation quite analogous to our Cats 29, 30, 38 and 40 (fig. 7). Brown then stimulated the cut surface with a unipolar electrode supplying a rapid induced current. From a strictly circumscribed area, 1 mm. in diameter, lying 3 mm. below the posterior commissure and 1 mm. from the midline, he elicited by stimulation a "most remarkable" reaction in respiration: "The normal slow, deep and steady respirations suddenly changed to a fast shallow breathing." Again, from another focal area, 4 mm. in diameter, which lies 2–3 mm. rostral to the caudal pole of the thalamus in the dorso-lateral margin of the neuraxis in its upper two-fifths, stimulation produced breathing which became vigorous and "hollow" with synchronous participation of the abdominal musculature. Reference to the diagram (fig. 8), which indicates the area we have found essential for decorticate polypneic panting in the cat, will demonstrate, in so far as analogy from one order to another be valid, that this area coincides with the focal areas outlined by Graham Brown.

Christiani (1885) investigated decerebrate rabbits and discovered that stimulation by electrical, thermal and physical agents of a discrete area 1 mm. square in the posterior thalamus, that is, in the lateral wall of the third ventricle immediately rostral to the superior colliculi and the commencement of the Sylvian aqueduct, evoked diaphragmatic arrest in inspiration or a remarkable acceleration of the respiratory rate. The area concerned here is once more the region to which we have drawn attention.

It is apparent that a search of the literature has revealed a considerable body of evidence that directly confirms our results. A recent report, however, by Frazier, Alpers and Lewy (1936) is in disagreement. These investigators employed a different experimental approach, using the Horsley-Clarke stereotactic instrument to place relatively discrete electrolytic lesions in the hypothalamus. They state that the lesions which destroyed the nucleus hypothalamicus anterior resulted in a complete deficiency in temperature regulation; and absent, too, was the polypneic panting usually observed in response to elevation of the body temperature. This is at variance with the data of Bazett, Alpers and Erb (1933), who found a polypneic deficiency when the

hypothalamus was intact but the caudo-dorsal part of the thalamus ablated. Careful inspection of figures (2 and 3) published by Frazier, Alpers and Lewy will offer an obvious explanation for this contradiction. These photographs show myelin sheath stains of coronal sections of the brain stems of the experimental preparations. It is quite evident that the area of damaged tissue far exceeds the discrete lesions assumed in the conclusions. The electrolytic needle was inserted through the hemispheres and pierced the thalamus in a vertical direction to reach the hypothalamus. The tract of the needle is rendered clearly visible by a blood-filled channel and adjacent demyelinized tissue which passes from the habenular region to the electrolytic lesion at the base. This tract of traumatized tissue passes directly through the dorsal thalamic area which we have shown to be so intimately concerned in the mediation of polypneic panting. It seems probable that this injury explains the absence of polypneic panting noted in their preparations. If so, it constitutes a cogent explanation for this apparent disagreement with the results which we have reported.

Having established, therefore, the presence in the posterior diencephalon of a neural center requisite for polypneic panting, it is of interest to examine the relationship of this respiratory function to other activities known primarily to depend upon this general region of the neuraxis for their neural integration and execution.

As first described by Cannon and Britton (1925) and by Bard (1928), the sham rage (quasi-rage) of a decorticate cat included among its manifold somatic and sympathetic manifestations the presence of polypneic panting. However, an examination of the detailed experimental protocols offered in these reports will make evident the fact that, during the quiet phases intervening between bursts of pseudaffective activity, polypneic panting continued. Furthermore, that the activities, which together constitute the quasi-rage phenomenon, are not invariably associated with polypneic panting, is further indicated by Cannon and Britton's specific observation that the onset of activity was characteristically associated with a deceleration in the respiratory rate (see their table I and figure 1). We have described above the change in respiration which heralds and then accompanies the advent of a phase of pseudaffective activity; and we have pointed out that it replaces, for the duration of the sham rage episode, the

background of polypneic panting. The converse of this state is, of course, the maintenance of polypneic panting while the animal is quiet. This is interpreted as a *physiological* dissociation of sham rage from polypneic panting.

The dissociation of these two phenomena may be effected likewise in an *anatomical* sense; for we have demonstrated that the neural structures requisite for the expression of rage (Bard) do not coincide spatially with those necessary for polypneic panting. Ablation of the caudo-*ventral* fourth of the diencephalon abolishes the capacity for the complete expression of rage; ablation of the caudo-*dorsal* fourth of the diencephalon abolished the capacity for polypneic panting. And this is proved by a varying series of transections which preserve both, one or neither of these reactions.

The phenomenon of decorticate polypneic panting at normal or subnormal temperatures requires some comment. As a working hypothesis, we have assumed it to be kindred to the Jacksonian "release" phenomena so frequently encountered when a phylogenetically new structure is ablated from the central nervous system, and the underlying reaction pattern of the phylogenetically ancient structures is uncovered. To assume that a reaction is one of "release," one must demonstrate that there are dominant structures from which release has been effected. In the case of decorticate polypneic panting, there is good evidence to indicate that the cerebral cortex plays a readily demonstrable rôle in the regulation of respiration, both to accelerate and decelerate the rate. Stimulation experiments have been numerous. Spencer (1894) reported the localization of cortical areas in the monkey, dog, cat and rabbit which, when stimulated, affect the respiratory rate; he reviews the bulk of investigation upon this problem which had been published at that date. More recently Bucy and Case (1936) have delimited inhibitory areas in the cerebral cortex of man and dog which, under electrical stimulation, produce marked deceleration of respiratory rate. Ranson and his co-workers (Kabat, Magoun and Ranson, 1935), employing the Horsley-Clarke stereotactic instrument within the neuraxis of the cat, have found discrete areas stimulation of which produces a decrease in respiratory rate. They found that stimulation of certain areas produced an abrupt fall in respiratory rate and blood pressure, lasting for the duration of the stimulus. These areas appear to constitute a tract arising in the gyrus genualis which,

extending into the subjacent white matter, passes through the genu of the corpus callosum and the structures ventral to it (including the gray matter medial and dorso-medial to the olfactory tubercle), through the gray matter about the anterior commissure and within the septum pellucidum and the medial preoptic area. This pathway coincides with the tractus neocorticoseptalis of Wallenberg (1934). These data offer convincing and varied evidence of the rôle played by the cerebral cortex in the control of respiration, and further, they present factual substantiation for the original assumption that there do exist higher inhibitory centers release from which results in decorticate polypneic panting.

SUMMARY

I. In the acutely decorticate cat, following withdrawal of ether anesthesia, there occurs a respiratory phenomenon termed *decorticate polypneic panting*, which ensues spontaneously at normal body temperatures. Polypneic panting is characterized by: a rapid rate (100-300 a minute), decreased amplitude of respiratory movements, open mouth, and rhythmic movements of the tongue and labial commissures synchronous with respiration.

II. Decorticate polypneic panting is modified in rate by changes in the body temperature of the animal. The rate varies in the same direction as the change in temperature. Furthermore, in decorticate cats which do not pant spontaneously, elevation of body temperature by artificial measures will induce polypneic panting.

III. By varying planes and levels of transection, it has been shown that the neural centers or connections requisite and sufficient for polypneic panting lie within the caudo-dorsal portion of the diencephalon.

IV. Decorticate polypneic panting is a phenomenon distinct from sham rage by virtue of its physiological dissociation and its separate anatomical center.

V. The probability that decorticate panting falls into the general class of release phenomena has been pointed out.

It is a great pleasure to express our gratitude to Dr. Philip Bard, who suggested this problem, and who, with Dr. Clinton N. Woolsey, made possible its completion by helpful criticism and encouragement.

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A PEDIGREE OF HEREDITARY CATARACT, ILLUSTRATING SEX-LIMITED TYPE

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This pedigree of hereditary cataract with microcornea is presented because of its unusual features. These features are (1) the affected males suffer from marked reduction of vision, whereas the affected females have either normal or but slightly reduced vision; (2) throughout three generations the affected members exhibit three types of cataract, one type limited to the males and the other two types to the females; (3) in the affected males microcornea is pronounced, while in the affected females the corneae are either of normal size or only slightly less than normal; (4) an example of an interesting triple race intermixture of White, Negro and Indian.

The family under consideration is one of a group of families with mixed White, Negro and Indian ancestors. They live in several counties in Southern Maryland and are known locally as "Weesorts," a name said to have originated from the practice of the individuals concerned calling themselves "we sorts." Similar intermixtures have been found and described elsewhere, notably in Virginia (1).

The pedigree is based on information from the persons described. General physical and ophthalmological examinations are briefly stated.

MEMBERS OF THE PEDIGREE

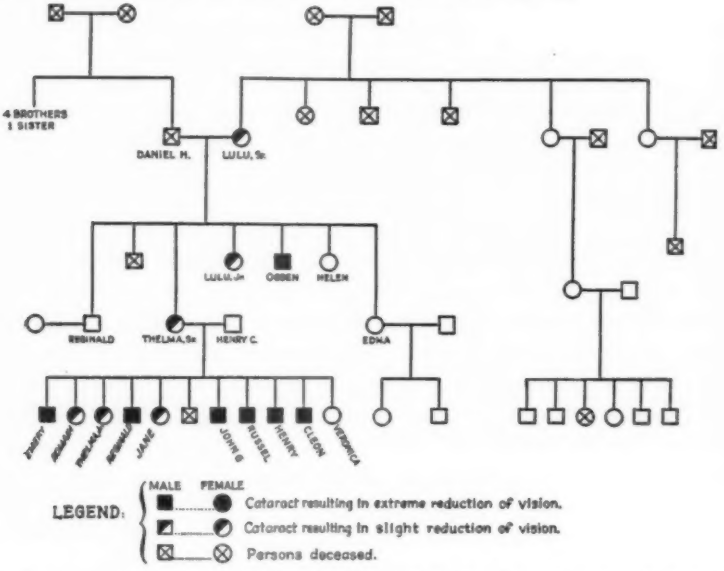
First generation

Lulu H. Sr., 63 years old, the maternal grandmother of the family of chief interest, was a vigorous, well preserved woman whose features were suggestively negroid and whose skin was very light brown. She had no congenital defects.

Her hair was fairly long, grey, and showed little tendency to kinking. She did not complain of any visual defect.

External examination of the eyes did not reveal any abnormality other than arcus senilis. The corneae appeared to be of normal size. R.E.V. = 20/20. L.E.V. = 20/100, 20/20 with pinhole aperture. Examination with an ophthalmoscope showed a few cortical opacities of each lens, and was otherwise negative. Slit-lamp examination showed, in addition, an opacity extending along the posterior Y suture line of the lens of each eye.

Daniel H. was the husband of Lulu H., Sr. He died at 59. He was described by his family as having been almost white in appearance except for kinky blond hair. He was said not to have had any general or ocular defect.



It is rumored that he was a half-brother to Lulu H., Sr., and that their father was a white man.

Second generation

Thelma, 37 years of age, daughter of Lulu H., Sr., and Daniel H., and mother of the family of chief interest, resembled her mother and her younger sister. Her hair was straight, brown-black and her features were only slightly negroid.

She did not complain of defective vision of her right eye. Her left eye had been injured during childhood. This injury resulted in the formation of a traumatic cataract, bound-down iris, loss of vision excepting perception of light, and out-

ward deviation of the eye of about 20°. The right cornea looked smaller than normal and measured 10.5 mm. in its transverse diameter. R.E.V. = 20/20. L.E.V. = perception of light. Ophthalmoscopic examination of the right eye revealed a lens opacity which was deeply situated and small. The fundus was otherwise normal. Slitlamp examination of this eye showed an opacity extending along the posterior embryonic suture line with an additional opacity—the opacity seen with the ophthalmoscope—below and slightly posterior to the Y suture. This slitlamp picture was identical with that observed in one eye of her daughter and namesake, as shown in Figure 1.

Lulu Marie, 31 years old, an unmarried sister of Thelma, Sr., resembled her closely, but was perhaps less negroid in appearance. The color of her skin was

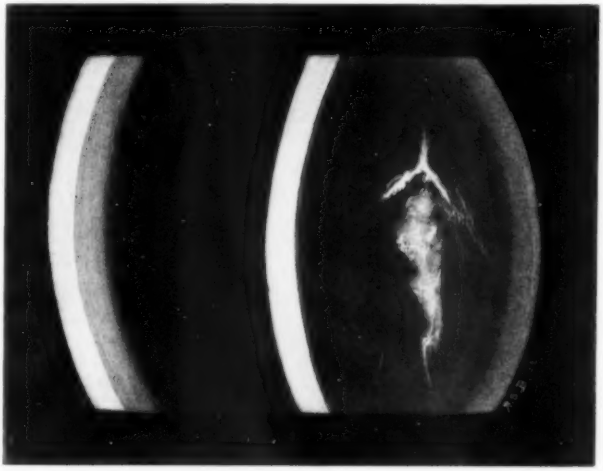


FIG. 1

the same as that of Thelma. She showed minimal signs of mitral stenosis and had a history of rheumatic fever.

She did not complain of poor vision. Her eyes appeared normal on external examination. R.E.V. = 20/20. L.E.V. = 20/100, not improved with lenses. Ophthalmoscopic examination showed a faint central opacity of the right lens and a denser linear opacity in the same region of the left lens. The slitlamp showed an opacity along the posterior embryonic suture line of the right lens and a similar opacity of the left lens where there was, in addition, a semicircular opacity embracing the posterior Y suture and extending forward with horn-shaped extremities almost reaching the anterior capsule (Figure 2).

Ogden, 30 years old, an unmarried brother, is best described by studying his

photograph. He did not show any congenital defects excepting the ocular abnormality. The skin was similar to that of his sisters described above (Figure 5).

He had had defective vision since birth. At 9 years of age a cataract extraction was done on both eyes. This resulted in a slight improvement in vision. There was bilateral microcornea, irregular and inconstant nystagmus, and bilateral operative aphakia. The lid slits were narrowed. The corneae measured 9 mm. in their transverse diameters. The anterior chambers were deep. The pupils were round and reacted actively to light. R.E.V. and L.E.V. with S^{+} 10.00 = counts fingers at 6 feet. Ophthalmoscopic examination was difficult because of the nystagmus. There was a small amount of capsular material in each eye. The discs appeared normal and the maculae were normal.

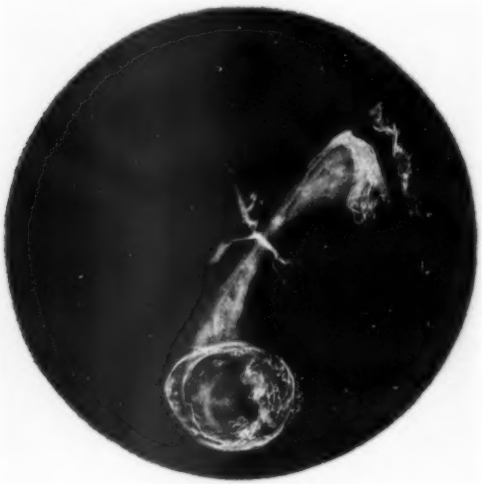


FIG. 2

Reginald, 38 years old, could easily pass for white, although his blond hair showed a tendency toward kinking. His skin was that of a sun-tanned person. He did not show any congenital defects. He is married to a mulatto. They have not had children, although contraceptives have not been used.

External examination of the eyes was negative. The vision in each eye was 20/20. Ophthalmoscopic examination of the eyes was negative. The slitlamp examination was not done.

Helen, 29 years old, unmarried, could easily pass for white. She did not present any obvious abnormalities. Examination of her eyes was negative externally,

as was the ophthalmoscopic and slitlamp examination. Her vision was normal in each eye.

Edna May, another sister who lived in Washington, could also pass for white. She and her two children, a boy of 6 and a girl of 2, were examined by Dr. Franklin Maury. The visual acuity of the mother and son was found to be normal, and that of the daughter seemed normal. A complete eye examination failed to reveal any abnormality.

A boy belonging to this generation died in childhood. He was thought to have been normal and similar to his brother Reginald in appearance.

Henry C., husband of Thelma and father of the family of principal interest, was a rather coppery mulatto with a pronounced Indian cast to his negroid features. His grandfather was half Indian. General examination and complete ophthalmological examination were negative.

There was no history of any of his relatives having had any ocular defects. His father, sister, brother, and nephew showed no ocular defects, but slitlamp examinations were not done.

Third generation (Children of Thelma and Henry C.)

Emory C., a boy of 16, resembled his father. He had suffered from greatly reduced vision all his life. This defect was noticed by his mother when he was two or three months old, but lens opacities were not observed until he was five or six months old.

External examination showed bilateral microcorneae, nystagmoid jerkings on efforts to fixate light, and a shining white opacity in the pupillary space of each eye. The corneae measured 10 mm. in their transverse diameters. R.E.V. = 7/200. L.E.V. = 7/200 (eccentric fixation) not improved with lenses. He could read ordinary print when held very close to his eyes. Dilatation with atropine did not improve distance vision. Ophthalmoscopic examination showed bilateral large lamellar cataracts, but was otherwise negative. Examination with the slitlamp showed that in the right eye the opacity surrounded a central clear area. From the main mass of the opacity an anterior projection reached almost to the anterior capsule, and an inferior band-shaped projection extended forward, while a wide projection extended backward. The cortex was studded with tiny white dots (figure 3). The slitlamp picture of the left eye was similar to that of the right eye, but the lens opacity did not surround a clear center.

Reginald, 12 years old, had the skin of a mulatto. He had straight, coarse, black hair, dark eyes, and high cheek bones.

His eye history was the same as that of Emory. External examination showed bilateral cataracts, and a fairly well developed epicanthus. The cornea measured 9.5 mm. R.E.V. = 7/200. L.E.V. = 7/200 (eccentric fixation). He could read ordinary print when held almost against his eyes. Glasses or dilatation of the pupil failed to improve distance vision. Ophthalmoscopic and slitlamp examinations showed the presence of a cataract in each eye. The cataracts were similar to those seen in Figure 3.

Romaine, 14 years of age, was more definitely of negroid type than any other member of the family. Her skin was quite dark and her hair kinky (Figure 5).

Examination of the eyes revealed bilateral epicanthus. There was a slight degree of microcorneae, each cornea measuring 10.5 mm. R.E.V. = 20/100—with pinhole aperture 20/20. L.E.V. = 20/100—with S −3.00 = 20/40. Ophthalmoscopic examination of the right eye showed an opacity of the lens that appeared to be placed in the anterior Y suture from consideration of its shape. Examination of the left lens showed a more diffuse opacity deeply situated. This examination was negative, otherwise. Slitlamp examination showed that the

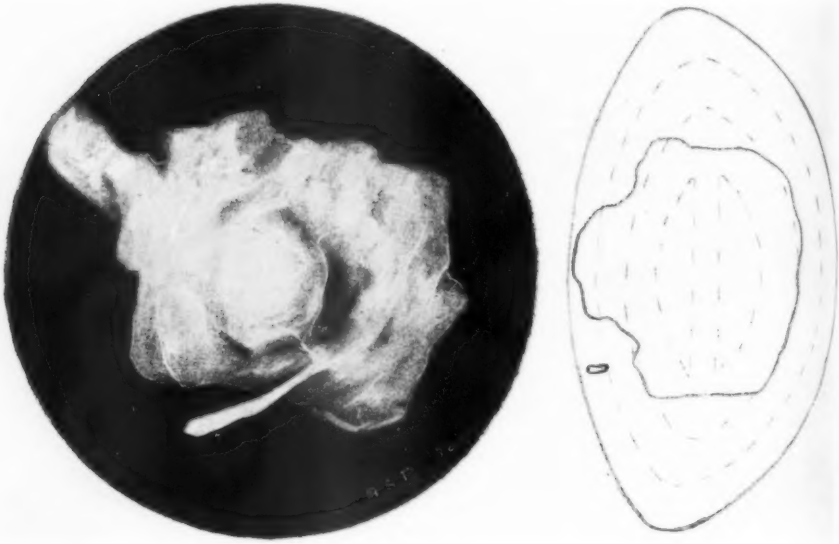


FIG. 3

y-shaped opacity in the right lens was behind the posterior embryonic suture which itself was the site of a less pronounced opacity. Scattered throughout the central portion of the lens many punctate opacities were seen. The lens opacity of the left eye, while more extensive, was similar to that of the right eye in that the main part of the opacity was situated behind the posterior embryonic suture. There were additional opacities extending into the adjacent lens.

Thelma, 13 years old, stood about midway between Romaine and Jane in appearance (Figure 5). She did not complain of visual defects.

Externally her eyes appeared to be normal. R.E.V. = 20/20. L.E.V. = 20/20. Ophthalmoscopic examination showed a deeply placed linear opacity in

the lens of the right eye and a Y-shaped opacity deep in the lens of the left eye. Examination with the slitlamp showed that in the right eye the opacity was in the region of the posterior embryonic suture, which also was the site of a less well defined opacity. In the left eye a Y-shaped opacity was seen to be deep to the posterior embryonic suture line (Figure 4).

Jane, aged 10, resembled her mother in appearance, particularly as to the color of her skin and condition of her hair (Figure 5).

She showed a slightly developed epicanthus bilaterally. External examination of the eyes was negative otherwise. R.E.V. = 20/20. L.E.V. = 20/20. The ophthalmoscope revealed a faint linear opacity of the lens of the right eye, deeply

FIG. 4

situated, and a still smaller and fainter opacity in the central portion of the left lens. Slitlamp examination was not done.

John, aged 6, Russell, aged 4, and Henry, aged 2, were alike in appearance. They were mulatto in type with kinky hair and dark brown skin.

These children were examined in the country. They exhibited bilateral microcornea with an estimated corneal measurement of 9 mm. All had cataracts, nystagmus and eccentric fixation. Their vision could not be accurately taken, but was approximately 5–15/200. Ophthalmoscopic examination with pupils dilated showed cataracts similar to, but less advanced than, those described in Emory and Reginald.

Cleon, a boy 1 year old, had white skin and slightly kinky blonde hair. He could easily pass for white (Figure 5).

His eyes were similar to those of John, Russell and Henry.

Veronica, 3 months old, had the appearance of a dark complexioned white baby of the Mediterannean races. Her hair tended to be kinky, but was soft.

Her eyes appeared normal on external examination. The ophthalmoscope did not reveal any defects. The ocular fundi appeared normal. Slitlamp examination could not be done.

FIG. 5

Top row: Thelma and Cleon, Lula H., Sr., Ogden
Bottom row: Reginald, Thelma, Romaine, Jane

COMMENT ON PEDIGREE

The cataracts in the affected males may be described as lamellar, zonular or perinuclear. The history indicates that the cataracts in the affected males rapidly increased in size shortly after birth. This is a frequent occurrence, as recently restated by Clapp (2). The cataracts in the affected females, because of their perinuclear situation,

may be considered as belonging to the same general group as those in the males, but they obviously are different in type and are either (1) posterior cataracts which could be detected only by examination with the slitlamp or (2) posterior stellate cataracts (Vogt, 3).

Variations in type in lamellar cataract are observed frequently, according to Waardenburg (4) and others, and furthermore these types of cataract may be hereditary. However, to our knowledge, a sex-limited distribution of type of cataract as observed in this family has not hitherto been described.

There are several pedigrees in the literature in which there appears to be sex-limitation or sex-linkage in hereditary cataract. Waardenburg mentions the family described by Stieren, and believes that in this family there was transmission of cataract as a sex-linked recessive. Stieren found 17 of 37 males affected in three generations. N. Bishop Harman (5) in the "Treasury of Human Inheritance" reproduced (a) the pedigree reported by Galezowski in which through four generations zonular cataracts were found to be limited to males; (b) the pedigree of Storbeck's family in which the children resembling the mother were free of cataract and those resembling the father were affected; (c) Dyer's pedigree in which congenital or infantile cataracts, becoming worse later in life, affected four generations and were confined to males. These pedigrees illustrating sex-limited inheritance of cataract are of interest in relation to the pedigree here detailed because sex-limitation in regard to type of cataract is of the same interest as involvement or non-involvement according to sex. On this point it may be mentioned that information from relatives indicated limitation to the male sex in the family here described. This proved not to be the case, and it is possible that in the earlier pedigrees similar information was given too much credence.

The pedigree here reported supports Nettleship's (6) observation that lamellar cataract tends to be transmitted by the mother. He found in ten families with familiar lamellar cataract that descent was continuous through the mother in thirteen generations, and through the father in six generations. It has been generally accepted that cataract is usually transmitted as a dominant Mendelian character, but this cannot be demonstrated in this pedigree. Dr. C. W. Metz of the Carnegie Institution of Washington, in considering this pedigree,

wrote: "It is difficult to interpret the genetic behaviour exhibited by this cataract on the basis of available data. In the first generation showing the affected individuals (offspring of Lulu H., Sr.) the results are essentially what would be expected in the case of a simple dominant character. But in the subsequent generation, in which nine of the ten known children—and presumably the tenth also—are affected, there is a wide deviation from expectation on this basis, unless we assume that the father or maternal grandfather carried and transmitted the dominant gene. The evidence is all against this assumption. Rather than speculate on the possible genetic basis of the character at present it seems desirable to await the appearance of another generation, which ought to provide significant information." This opinion applies also to the genetics of the microcornea and epicanthus.

Although the diameters of the corneae of the affected males were definitely below the average of 11.6 mm. as given by Ida Mann and the diameters of the cornea of two affected females were somewhat smaller than normal, no conclusions were arrived at regarding the size of the posterior segments which appeared to be of about normal size. Thomsen (7), among others, has drawn attention to the difficulty in deciding whether or not the posterior segment is altered in size in microcornea. In the examination of this family an accurate measurement of the size of the cornea was made only once (Emory) when calipers were used. The other measurements were made with a millimetre rule or by estimation. Lenses did not improve the vision in two of the boys (Emory and Reginald), but refraction was not attempted with the other boys. A −3.00S improved the vision in one affected female (*Romaine*).

The racial characteristics of several of the members of the family are shown in photographs of some of them. Any attempt to analyze these characteristics, because of the incompleteness of available information, would be futile.

SUMMARY

Three of six members of the first generation were alive. All three were examined. No member of this generation was thought to have had defective vision. One individual, the grandmother of the family of principal interest, was affected although her vision was normal.

Examination with the slitlamp showed that she had posterior suture cataracts. Some of her descendants inherited cataracts, but her unaffected siblings did not transmit cataracts.

Six of seven members of the second generation were alive, and all six were examined. One male and two females were affected, and one male and two females were free of the defect. The affected male showed bilateral operative aphakia, pronounced microcornea and nystagmus. One of the affected females, on examination, showed a posterior suture cataract in one eye and a posterior stellate cataract in the other eye. The other affected female, the mother of the family of principal interest, exhibited a combination of posterior suture and posterior stellate cataract in her uninjured eye.

Ten of eleven members of the family of chief interest were examined. One sibling, a male, died three days after birth. Of the ten living siblings six were boys, all of whom exhibited the defect. They showed manifest lens opacities, which were of sufficient size that they appeared to fill or almost fill the pupillary space, microcorneae and nystagmus. Three of the four females, on examination, were found to have lens opacities which in one individual were posterior suture cataracts, and in another a combination of posterior suture and posterior stellate cataracts. The third female was not examined with the slitlamp, but was seen to have posteriorly situated perinuclear opacities. The two months old baby girl, also examined only with the ophthalmoscope, seemed to have clear lenses, but without a slitlamp examination the presence or absence of suture cataracts could not be established.

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SULFANILAMIDE RASH

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Quite a number of drugs, especially those containing the benzene ring in their molecular structure, are known occasionally to produce a cutaneous eruption. During the course of treatment with sulfanilamide, we have observed in a number of patients the development of a rash which we believe to have been caused by the drug.

The sulfanilamide was administered to a total of 180 patients both orally and parenterally. Infants up to 40 pounds of body weight were given 2.0 to 2.4 grams per day; children weighing 40 to 80 pounds, 3.0 to 3.6 grams and adults, over 80 pounds in weight, 4.0 to 4.8 grams daily. Fifty-six of the patients were suffering from meningococcus meningitis; the remainder from some form of infection due to the beta hemolytic streptococcus. Of the 180 patients treated 10 (6 per cent) developed a rash. The relationship between duration of the treatment and the time at which the rash appeared is shown in table 1. Although in some cases it was recognizable as early as the third day of sulfanilamide medication, in half of the cases it appeared between the tenth and fourteenth days.

The eruption (fig. 1) is distinctly morbilliform in character, made up of maculo-papular lesions slightly raised from the surrounding unaffected skin and brownish-red in color. Although it does not fade completely when pressure is applied, the blanching of the rash is considerably more marked than that seen with a typical measles eruption. Usually almost the entire surface of the body is affected, but in some cases the rash has been limited to the buttocks or to the legs. In some of our patients the eruption was seen on the palms of the hands and the soles of the feet while the mucous membranes were apparently

unaffected. There was no itching or other abnormal sensation at the site of the lesion.

The rash usually develops rapidly without any prodromal symptoms, the entire evolution occupying only about 12 hours. Fever and general malaise have always been present and have sometimes preceded the eruption by several hours. The temperature rises suddenly, usually ranging between 101° and 103°F., and then drops to normal gradually over a period of 2 to 4 days. The malaise disappears with the fever. No other symptoms or signs have been observed. The blood count shows no significant alteration.

TABLE 1

Time of development of sulfanilamide rash in relation to period of treatment

DURATION OF SULFANILAMIDE TREATMENT	NUMBER OF CASES	NUMBER OF PATIENTS DEVELOPING RASH	DAY OF TREATMENT ON WHICH RASH DEVELOPED
days			
1–4	36	3	3rd, 4th, 4th
5–9	109	1	5th
10–14	18	5	9th, 11th, 11th, 11th, 14th
15–19	9	1	17th
20–24	4	0	
Over 24	4	0	
Total	180	10 (6%)	

With discontinuance of sulfanilamide therapy the eruption fades rapidly and may disappear completely in 48 hours. If administration of the drug is now resumed, the rash sometimes reappears faintly or in scattered areas but never assumes its former brilliance, and even this slight recrudescence gradually fades away. In several patients a sharp febrile rise followed the resumption or sulfanilamide therapy. In one of these the secondary rash was erythematous and suggested scarlet fever. If the sulfanilamide treatment is not discontinued at the time of appearance of the primary rash, the eruption fades and disappears completely in about 72 hours.

Comment. There is no absolute evidence that the rashes we have observed are due to the sulfanilamide. The circumstantial evidence, however, is strong. The eruption has been seen only in patients re-

FIG. 1. PHOTOGRAPHS OF THE SKIN OF TWO PATIENTS SHOWING RASH DUE TO SULFANILAMIDE

ceiving the drug; and almost always after a definite period of treatment. It fades more rapidly when the administration of sulfanilamide is stopped than if it is continued. After the rash has faded it can be reproduced, in a somewhat modified form, by a renewal of treatment. Fever, which always accompanies the primary rash, reappears with the secondary eruption. And since other compounds containing the benzene ring in their molecule are known to produce similar cutaneous lesions, it is not surprising that they are observed with sulfanilamide.

ON THE CYANOSIS FROM SULFANILAMIDE

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Submitted for publication June 19, 1937

Cyanosis of varying degree is observed in a large percentage of patients undergoing intensive treatment with sulfanilamide (para-aminobenzenesulfonamide) (1). This cyanosis has been attributed to the presence of methemoglobinemia or sulfhemoglobinemia (2). We have examined the blood from seven patients treated with sulfanilamide in an attempt to determine how far the oxygen carrying capacity of the blood is reduced in patients showing cyanosis. The oxygen carrying capacity was compared with the total iron pigment of blood.

The active hemoglobin was determined by means of oxygen capacity after saturation of the blood with air (3). Duplicate determinations were done. The total iron blood pigment was estimated by an iron determination by the dipyridyl color reaction after a digestion of the blood with sulfuric and nitric acids (4). The blood was diluted five times with water and 0.5 or 1.0 cc. taken for a determination. It was found necessary to accurately standardize the solution of ferrous ammonium sulfate used as a standard. Triplicate determinations were always done. The difference between the above values gives the non-functional iron pigment regardless of its nature. We have considered differences of a 0.5 volume per cent of oxygen or less as possibly due to the experimental errors of the two methods. In certain instances a determination of hemoglobin plus methemoglobin was made by the method of Van Slyke and Hiller (5) and the blood examined for abnormal pigments by means of the spectrophotometer. The results are given in table 1. The third column indicates by a plus (+) or minus (−) sign whether or not cyanosis was present in the patient; the fourth column gives an estimate of the dark color of the blood after saturation with air, a minus (−) sign indicating a blood of normal red color, and the number of plus signs the degree of darkness; in the last column the minus sign indicates the absence of all absorption

bands except those of oxy-hemoglobin, the plus sign indicates an absorption band with its maximum at the wave length of 630 mμ; the

TABLE 1

	DATE	CYANOSIS	DARK COLOR BLOOD	VOLUMES PER CENT OXYGEN			SPECTROPHOTOMETER
				O_2 capacity	Iron	Hemoglobin + methemoglobin	
1. I. K. 12 yrs. 30.8 kgm. Subacute bacterial endocarditis. 4/5 to 5/19, 3.6 gm. per day, 5/19 on 5.4 gm. per day.	5/21	+	++	11.9	11.8	11.6	−
	5/25	+	++	11.9	11.9	11.9	−
	6/15	−	−	9.9	10.0		
2. L. B. 10 yrs. 25.2 kgm. Mastoiditis. 5/7 on 3.6 gm. per day.	5/21	+	+	11.3	11.2		
3. H. C. 20 yrs. 61 kgm. Lymphangitis. Drug started 6/1, received total of 23 gm. through 6/4.	6/3	−	+	20.5	21.0		
	6/4	+	++	19.1	19.0		−
4. H. A. 31 yrs. 58 kgm. Subacute bacterial endocarditis. Drug started 6/4, 4.8 gm. per day. 6/2 to 6/5, aspirin 2.7 gm. per day.	6/4	−	−	16.3	16.2		
	6/9	−	−	16.1	15.6		
	6/10	±	++	16.2	16.2		
5. C. K. 8 yrs. 28.8 kgm. Hemolytic staph. albus of genito-urinary tract. Drug from 6/7 on, 2.7 gm. per day.	6/10	−	−	14.1	14.5		
6. E. H. 17 yrs. 47.5 kgm. Subacute bacterial endocarditis. Drug started 12/16/36. Has been receiving from 4.5 to 9.0 gm. per day. When blood was taken receiving iron by mouth.	5/21	+	+++	9.6	11.2		
	6/10	+	++++	11.4	12.8	13.2	
7. A. W. 19 yrs. 59 kgm. Acute rheumatic fever. Drug started 5/27, 3.6 gm. per day. Aspirin 4.8 gm. per day.	5/27	−	−	15.7	15.6		−
	5/31		++	17.3	17.8	17.4	−
	6/3	+	+++	16.0	16.9	16.1	−
	6/8	+	++	13.2	14.6	14.1	+
	6/9	+	++++	14.3	15.0	15.1	
	6/15	+	+++	13.3	13.5		

oxygen capacity (active hemoglobin), iron, and hemoglobin plus methemoglobin are all calculated in terms of volumes per cent oxygen.

It is to be noted that in cases 4 and 7, a control sample of blood was examined before administration of the drug was started.

The most significant conclusions to be drawn from the data of table 1 are that clinical cyanosis may be unaccompanied by any decrease in the oxygen carrying capacity of the blood and may occur without the presence of non-functional iron pigment within the errors of the methods employed. Only in cases 6 and 7 do the figures indicate non-functional iron pigment. This non-functional iron pigment appears to be mainly methemoglobin, as it is reduced to hemoglobin by alkaline hydrosulfite and gives an absorption maximum at the wave length characteristic of methemoglobin ($\lambda = 630$ mμ). It is to be noted that patient no. 7 was receiving large doses of acetylsalicylic acid, and that no. 6 had received large doses of sulfanilamide for about seven months. The possibility of methemoglobin being present in small amounts in the blood samples from the other cases cannot be disproved by our data. However, an average of the figures for the five instances in which neither cyanosis nor a dark color of the blood was present gives 14.42 volumes per cent from the oxygen capacity and 14.39 from the iron content; and an average of the figures for the six instances in which dark blood was present (excluding cases 6 and 7 on account of methemoglobin being present) gives 15.15 volumes per cent from the oxygen capacity and 15.18 from the iron content. This makes it unlikely that more than traces of methemoglobin were present in these bloods. The addition of 0.5 volume per cent of methemoglobin to a normal blood was found to change the color very little, if at all. Methemoglobin as the cause of the cyanosis and dark color of the blood can be eliminated in the first five patients, and also probably as the only cause in cases 6 and 7.

Of course, from the data on the few cases studied, we cannot deny that sulfhemoglobin as well as methemoglobin may occur under certain conditions after administration of sulfanilamide, but it seems clear that these abnormal iron pigments supply by no means the only, and probably not the main, explanation of the cyanosis so frequently encountered in using the drug.

About fifty years ago, Engelhardt (6) in a study of aniline poisoning in the cat concluded that the cyanosis and dark color of the blood was due to the presence of methemoglobin and of a bluish-black pigment

derived from aniline and presumed to be aniline black. More recently, Young and Wilson (7) failed to find methemoglobin in rabbits during aniline intoxication, although cyanosis and dark blood were observed. The blood, however, became red on prolonged shaking with air. They supposed that para-aminophenol or some of its oxidation products might be partly responsible for the cyanosis. Payne (8) found that in acetanilid poisoning the gray discoloration of mucous membrane and skin and the brownish color of the blood in both dog and man persist long after methemoglobin and sulfhemoglobin have disappeared. He considered that this may be due to para-aminophenol, since accumulation of a foreign brown pigment is observed microscopically in the tissues. It is quite possible that in the case of sulfanilamide the cyanosis and dark color of the blood are due to the presence of a black oxidation product of the drug which stains the red blood cells. Treatment of sulfanilamide with calcium hypochlorite solution in the cold produces first a yellow, then a reddish and finally a black oxidation product. We have made attempts to extract a pigment from these dark-colored bloods with various organic solvents, but have so far been unsuccessful.

SUMMARY

An investigation of the oxygen capacity and total iron pigment of the blood of patients receiving sulfanilamide indicates that the cyanosis may not be due to non-functional iron pigment. In some instances small amounts of methemoglobin were found, but it is questionable if this is the principal cause of the cyanosis.

We are indebted to Miss Dorothea Babbitt for the iron analyses, and to Drs. P. H. Long and H. Shwachman for obtaining the bloods from the patients.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Abortion, Spontaneous and Induced; Medical and Social Aspects. By FREDERICK J. TAUSSIG. 536 pages. Illustrated. $7.50. (*C. V. Mosby Company, St. Louis, 1936.*)

In this book the author aims to "help the practitioner and specialist in medicine in the diagnosis and treatment of various forms of abortion, and give to the sociologist and student of public health the facts necessary to understand the way in which abortion undermines the physical well-being and moral integrity of the community." It is pointed out that one out of every three or four pregnancies terminates in abortion; eight to ten thousand young women lose their lives from this cause every year.

The usefulness of the present work is aided by a bibliography of more than 700 titles, nearly 150 illustrations, and a comprehensive index.

F. F. S.

Childless. By SAM GORDON BERKOW, M.D. Illus. Pp. 307. $3.00. (*Lee Furman, Incorporated. Publishers, New York, 1937.*)

The author, a medical man, summarizes for lay consumption our knowledge of sterility. The book opens with all too scant an introduction, presenting the history and folklore of his topic. It then discusses the sex cells, safe period, endocrine factors, influence of food on fertility, venereal disease, and the prophylaxis and treatment of sterility. The book is a competent but not distinguished contribution. There are many scientific errors which shake one's confidence. For example, the author states that the egg probably survives for eight *days* after ovulation, although all reliable data make eight *hours* more likely. He then states that "menstruation and ovulation may or may not be synchronous." Certainly the preponderance of evidence refutes this possibility. The book is greatly strengthened by the inclusion of a good bibliography and index.

A. F. G.

The Intimate Side of a Woman's Life. By LEONA W. CHALMERS. Pp. 128. Ill. Price $1.50. (*Pioneer Publications, Inc., New York, 1937.*)

This book is written by a lay woman for lay women. The author shows an amazing unfamiliarity with the scientific aspects of her topic and with scientific methodology. The work is surcharged with incredible overstatement and false evaluation of data. For example, she lays the corner stone of all female ills on constipation—the improper evacuation of the colon, "the garbage can of the

human body," and on leukorrhea, "the thief of womanly charm." The author has a commendable and sane attitude toward sex education which is the saving grace of her treatise.

A. F. G.

Dietetics Simplified. By L. JEAN BOGERT AND MAME T. PORTER. 637 pp. Illus. $3.00. (*The Macmillan Company, New York, 1937.*)

A comprehensive survey of dietetics in a very readable form. A well balanced combination of scientific data and practical information make it a good textbook for the student of Home Economics or the student nurse. The dietitian will find it valuable for a ready reference. Because this book is so simply written, it would interest the lay person and teach without confusion.

The authors give first a careful explanation of the requirements of the normal diet of the adult, the infant and the child, discussing the influence of cost and of racial food customs. Diet therapy, laboratory lessons in cookery and laboratory projects in diet and disease are treated successively. Tables of the nutritive value of foods, weights and measures, height, weight, age charts and recipes are to be found in the appendix.

H. B.

William Withering: The Introduction of Digitalis into Medical Practice. By LOUIS H. RODDIS. 131 pp. Illus. $1.50. (*Paul B. Hoeber, New York, 1936.*)

This little book presents a satisfactory outline of the life and diverse accomplishments of William Withering, physician, botanist and mineralogist. The story of his great contribution to the treatment of heart disease, the introduction of Foxglove or Digitalis into medical practice is adequately recorded, and fortunately the last section of Withering's Treatise "An Account of the Foxglove and Some of its Medical Uses" is reprinted with a facsimile of the title page. The titles of the paragraphs in this last section read as follows: "Of the Preparations and Doses of the Foxglove"; "Effects, Rules and Cautions"; "Constitution of Patients," and "Inferences". It is surprising to discover with what preciseness Withering wrote these directions, how accurately he described his results, and with what caution he warned against the toxic effects of the drug. Some inkling is given, too, by Commander Roddis in his little volume of Withering's many interests, and sufficient is said about his important accomplishments as a botanist and his observations upon mineralogy to indicate that it was not exclusively in the practice of medicine that he made contributions that attracted widespread attention.

One can read between the lines, which are concerned very largely with factual data, collected it seems, at times, somewhat at random, the character of this talented country gentleman, but the reader wishes that he might be told more of Withering as a person and be left, even in the short space available, with a picture of the man said to have been "The Flower of Physic" as well as with a description of his accomplishments.

There are several illustrations including a copy of the portrait by Von Breda which forms the frontispiece of the book. The little volume is well printed and neatly bound.

W. T. L.

Heart Disease. By PAUL DUDLEY WHITE. 2nd ed. 744 pp. Illus. $7.50. (*The Macmillan Company, New York, 1937.*)

Since its first appearance in 1931, this book has been distinguished for the comprehensive manner in which the author deals with the pathology, diagnosis and treatment of heart disease. The broad scope of the first edition was reflected in the voluminous bibliography, which in itself occupied nearly two hundred pages. In the second edition the number of pages has been reduced from 931 to 744 despite the addition of new material, and a thinner paper has been used, so that it weighs a pound and a half less than the first edition. The first section dealing with methods of cardiovascular examination has been cut in half, the bibliography has been shortened to include only key references and these are now placed at the ends of the individual chapters. As a result of this extensive pruning, the book has gained tremendously in conciseness and suitability for use of medical students and physicians.

New material representing the advances of five years includes sections on acute *cor pulmonale*, the heart in trichiniasis and in von Gierke's disease. The chapter on congenital heart disease has been greatly improved by the addition of twenty pages dealing with individual congenital cardiovascular defects. The chest lead in electrocardiography, roentgenkymography, the carotid sinus reflex, thevetin and the association of hypertension with pituitary basophilism are among the subjects mentioned for the first time. Jaundice from pulmonary infarction in heart disease, overlooked in the first edition, has been noted.

There is no counsel concerning the use or avoidance of digitalis in the treatment of coronary thrombosis. Concerning typhoid vaccine therapy in chorea, the author merely states that it "may do more harm than good by inciting an attack of rheumatic fever (Bland and Jones 1935)." Since Bland and Jones worked with patients suffering from chronic rheumatic fever rather than chorea, it hardly seems justifiable to use their studies to discredit a form of therapy from which good results have been reported.

The many new illustrations, especially of roentgenograms of the heart, enhance the value of the new edition, and the dull cream paper adds to its readability. The author clearly sets forth many fundamental facts included under the concept of "Heart Disease", and designates the sources where more detailed and discursive information may be found.

C. B. T.

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON AND ROBERT P. MACFATE. 877 pp. Illus. $9.50. (*Lea & Febiger, Philadelphia, 1937.*)

Between the covers of a single volume, the authors have sought to place most of

the information of a laboratory character that a student or physician would have need to seek. Thus, not only are the usual microscopic and chemical procedures described, but numerous details of bacteriology, serology, skin testing and other biological tests, milk and water analysis, histological technique and medicolegal and toxicologic procedures are also given. Only medical entomology has been omitted. To this information are added brief statements concerning anatomy, physiology and clinical symptoms, with the object of indicating the purpose and value of the various tests considered.

On the whole, the work is satisfactory. In parts, however, one gains the feeling that we have here a compendium of methods rather than a critical digest. Thus various types of gastric acidity curves are given, without warning as to the possible misleading character of such information. Again, so many methods for chemical analysis of gastric contents are described that the reader is soon bewildered. In other sections, fuller treatment would probably have been desirable. The intestinal parasites are treated somewhat more fully than in the majority of clinical laboratory textbooks but a still more detailed account would, in the reviewer's opinion, have been more suitable in a work of this size. The difficulty of recognizing unfertilized ascaris eggs is not mentioned.

In a number of respects, recent advances in laboratory diagnosis are disregarded. Thus, although five tests of liver function are described, the bilirubin test is not mentioned. Again, the increasingly wide use of the sedimentation test merits discussion of interpretation in some detail. This, one seeks in vain. In the section on hematology, the blood values for normal adults, which were recorded 85 years ago, are still presented and the recent accurate data are completely ignored. This defect is made all the more evident by the thorough treatment this subject receives in the section on blood in infants and children. Physiologic variations in adults in erythrocyte count and hemoglobin receive no mention, and little attention is paid to the important subject of physiologic variations in leucocyte count. The elliptical cell anomaly is erroneously referred to as a form of anemia. In the section on serology, are repeated such ancient but erroneous statements as, "a high fever and anesthesia may produce a slight [Wassermann] reaction", "alcoholic drinks will occasionally produce a negative test for several days in a syphilitic patient", and a falsely positive reaction is mentioned as sometimes occurring in "cases of advanced sepsis, non-pulmonary tuberculosis, cancer, internal fungus infections, jaundice and severe diabetes."

There are 144 engravings and 13 plates, 5 in colors, the great majority of which are very useful.

M. M. W.

Psychiatric Social Service in a Children's Hospital. By RUTH M. GARTLAND. 105 pp. $1.25. (*The University of Chicago Press, Chicago, 1937.*)

At present Social Service in the treatment of patients differs from place to place and from doctor to doctor. Social service may be used as a substitute for or as a supplementary form of therapy. Miss Gartland's monograph illustrates its use in

direct treatment of patients. The first half of the study is concerned with an analysis of the cases of 132 patients, seen between October, 1932, and October, 1934, in the psychiatric clinic of the pediatric department of the University of Chicago Clinics. In the last two chapters Miss Gartland presents an illustrative case and her conclusions. The case demonstrates "changing treatment trends" in psychiatric social work. Miss Gartland believes the first social worker failed in the management of this case because her focus was upon "the intellectual study of problems (symptoms) and their causes," and that her approach was made to "meet her own needs" rather than those of the patient. The second social worker succeeded because she focussed on the people, patient and parents, rather than on their problems, and her attitude was "non-judgmental."

The conclusions seem to deal as much with the functions and administration of a psychiatric unit in a pediatric department as with psychiatric social work. In the Chicago clinic patients are referred from pediatrician to psychiatrist through the psychiatric social worker. Miss Gartland prefers "short diagnostic-psychiatric histories" to "long informative ones" in reporting back to the referring pediatrician. Such a method of reporting would tend to limit teaching values, and it is certainly open to question whether patients should not be referred directly from physician to physician rather than by way of a social worker.

Miss Gartland's experience as a teacher enables her to make suggestive, sometimes provocative, comments. These make the book worth reading.

M. M.

BOOKS RECEIVED

Synopsis of Pediatrics. By JOHN ZAHORSKY. 2nd. ed. 367 pp. Illus. $4.00. C. V. Mosby Co., St. Louis, 1937.

Contributions to the Microscopic Anatomy of the Pancreas. By PAUL LANGERHANS. [Berlin, 1869]. Reprint of the German original with an English Translation and an Introductory Essay by H. Morrison, M.D. 39 pp. Illus. $1.00. Johns Hopkins Press, Baltimore, 1937.

Trauma and Disease. Edited by LEOPOLD BRAHDY and SAMUEL KAHN. 613 pp. Illus. $7.50. Lea & Febiger, Philadelphia, 1937.

Handbook of Microscopical Technique. Edited by C. E. MCCLUNG. 2nd ed. revised. 698 pp. Illus. $8.00. Paul B. Hoeber, New York, 1937.

Précis de Physiothérapie Clinique. By PAUL DUHEM. 603 pp. Illus. 130 francs. Gauthier-Villars, Paris, 1937.

Surgical Treatment. By JAMES PETER WARBASSE and CALVIN MASON SMYTH, JR. 2nd ed. revised and reset. 3 vol. with separate index. 2617 pp. Illus. $35.00 set. W. B. Saunders Company, Philadelphia and London, 1937.

Infantile Paralysis and Cerebral Diplegia. By ELIZABETH KENNY. 125 pp. Illus. 21 shillings. Angus & Robertson, Sydney, Australia, 1937.

The Larynx and its Diseases. By CHEVALIER JACKSON and CHEVALIER L. JACKSON. 555 pp. Illus. $8.00. W. B. Saunders Company, Philadelphia and London, 1937.

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN. 6th ed. revised. 707 pp. Illus. $7.00. Lea & Febiger, Philadelphia, 1937.

Woman's Prime of Life. By ISABEL EMSLIE HUTTON. 150 pp. $2.00. Emerson Books, Inc., New York, 1937.

Psychiatric Social Service in a Children's Hospital. By RUTH M. GARTLAND. (University of Chicago Social Service Monographs). 105 pp. $1.25. University of Chicago Press, Chicago, 1937.

Maternal Care. Edited by DR. F. L. ADAIR. 93 pp. $1.00. Paper bound 25 cents. University of Chicago Press, Chicago, 1937.

Physicians and Medical Care. By ESTHER LUCILE BROWN. 202 pp. 75 cents. Russell Sage Foundation, New York, 1937.

Physical Diagnosis. By DON C. SUTTON. 495 pp. Illus. $5.00. C. V. Mosby Company, St. Louis, 1937.

Man in a Chemical World. By A. CRESSY MORRISON. 292 pp. Illus. $3.00. Charles Scribner's Sons, New York, 1937.

3

EXTRACELLULAR FLUID

Extracellular Fluid and Its Vicissitudes*

JAMES L. GAMBLE, M.D.

From The Department of Pediatrics, Harvard University Medical School

The extracellular body fluids may be described as the plasma of the blood and the interstitial fluid (including lymph) which lies between the vascular compartment and the tissue cells (fig. 1). Extracellular fluid constitutes, as Claude Bernard appreciated, the immediate environment of the organism. This aqueous medium which surrounds the tissue cells sustains two important services. One of these is conveyance of nutrient and waste materials. With this transport function we have long been familiar. The other service which extracellular fluid must provide, our understanding of which we owe largely to Lawrence Henderson, is a stability of physico-chemical conditions within the organism. Prominent among these are reaction, in terms of hydrogen ion concentration, osmotic pressure and temperature. The values for these properties in cell fluid rest on the values at which they are held in the surrounding medium. The necessity for nearly stationary values may be indicated by recalling that the rates at which processes of chemical change proceed are, to a widely varying extent, affected by change in degree of accompanying physical circumstances. It is therefore evident that the innumerable and interrelated chemical reactions, which together accomplish what we call metabolism, would rapidly fall out of adjustment if these underlying conditions were not held at fairly constant values.

The dimensions of the internal environment are stated in rough terms in figure 1. The quantity of blood plasma in the body is about 5 per cent of body weight. This information has been obtained by the familiar dye methods for measuring plasma volume. The quantity of interstitial fluid is here given as 15 per cent of body weight.

* Lecture I of the tenth course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in clinical medicine. Delivered at The Johns Hopkins School of Medicine, March 30, 1937.

This is an estimate which has been arrived at by several methods of approach which will presently be mentioned. The mechanics of the circulation of the blood make maintenance of a stationary volume in the vascular compartment of much more importance than in the interstitial space, and we find that the increase in volume of extracellular fluid which we call edema is covered by expansion of the

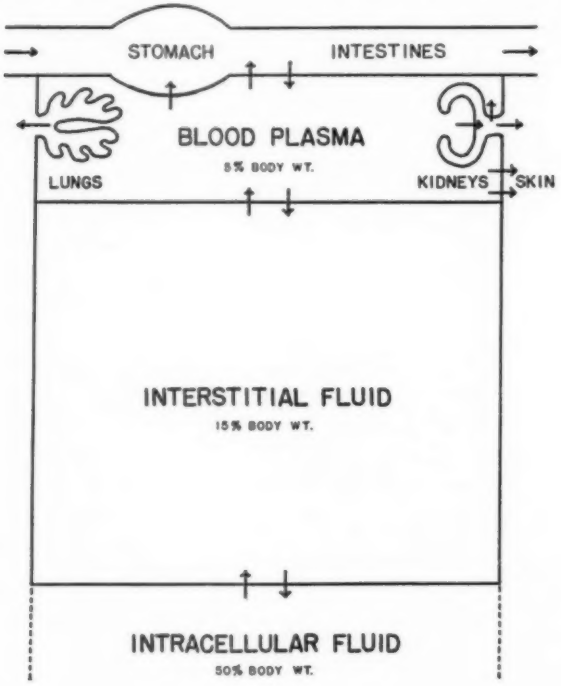


FIG. 1

interstitial space and that, on the other hand, plasma losses caused by processes of dehydration are replaced by interstitial fluid. The capacity of the interstitial compartment thus exhibits a wide adjustability in defense of blood plasma volume. We may here note that behind the plasma we have a reserve of fluid which is about three times the volume of the plasma.

The chemical anatomy of the extracellular fluids is described by the two middle diagrams in figure 2. In these diagrams the relative values for the electrolytes are shown in terms of acid-base equivalence. The values for the cations or potential base are superimposed in the

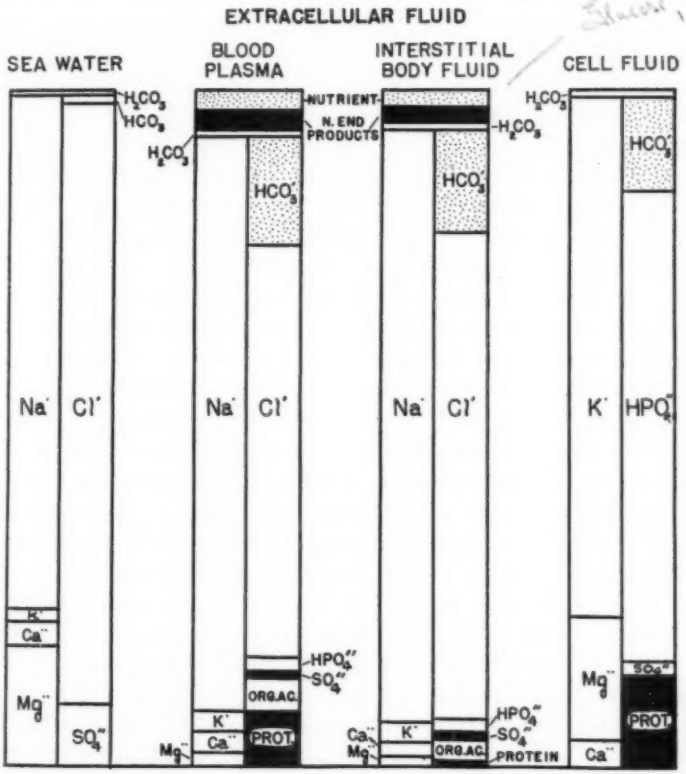


FIG. 2

left-hand columns and those for the anions or acid radicals in the right-hand columns. In the case of the univalent ions which make up the bulk of the electrolyte structure, chemical equivalence corresponds with ionic concentration. The chemical equivalence of the four divalent ions, Ca, Mg, HPO_4 and SO_4 is, of course, twice their concen-

tration values. So that, except for these four small items of structure, the relative values shown in the diagrams describe concentration as well as chemical equivalence. The line down the center of each diagram indicates appropriately that we have to deal not with salts but with separately controlled concentrations of ions. The relative values for the non-electrolytes, in terms of concentration, are placed across the diagram. The diagrams make clear the almost identical chemical structures of blood plasma and interstitial fluid. The small differences in the values of the ionic components are adjustments in terms of osmotic requirements to the much larger quantity of the non-permeating protein ion in the plasma. We may therefore properly regard extracellular fluid as a single fluid lying in two compartments equipped with a device (plasma protein) for producing movement from the interstitial space into the vascular compartment.

To mention very briefly the history of extracellular fluid; the first diagram in figure 2 describes the chemical composition of the aqueous medium in which the earliest forms of life developed. The resemblance of the electrolyte pattern of sea water to that of extracellular fluid is very striking. We find the same four components of the total base value, the same prominence of the concentrations of sodium and of chloride ion, and the same pair of buffering substances, free carbonic acid and bicarbonate. In other words the chemical skeleton of sea water is clearly visible in extracellular fluid. We find, to be sure, a number of additional substances. Such substances are, however, present in sea water in the vicinity of living organisms, but at concentrations too small to be visible in the sea water diagram. Their conveyance at appreciable concentrations is an understandable consequence of living in a small enclosed medium instead of in the wide ocean. The alterations of the chemical framework of sea water which their presence makes necessary are, however, relatively small. Sodium remains the backbone of the electrolyte structure. The larger bicarbonate concentration in extracellular fluid and the anions at the bottom of the acid column are supplied with space at the expense of the concentration of chloride ion. Chloride ion, however, remains the chief structural factor on the acid side of the diagram. The origin of the internal medium, long ago indicated by the work of Bunge and Quinton, has in our time been interestingly studied by Macallum (1).

That extracellular fluid is a surrounding and not a pervading medium is evident from the widely different electrolyte composition of cell fluid which is roughly described by the last diagram in figure 2. Here we find the base column almost entirely composed of potassium, and phosphate ion dominating the anions. According to this diagram the two large structural factors of extracellular fluid, sodium and chloride ion, are not permitted to pass the boundaries of protoplasm. We are not quite sure that this is the case, although we would like to believe that it is. The integrity of the chemical pattern of extracellular fluid and the stability of its physico-chemical properties rest in large measure, as I shall try to show you, on maintenance of correct quantities of sodium and of chloride ion. Accuracy of this control would, we may suppose, be facilitated by confining sodium and chloride ion to the extracellular compartments. Here, however, we are venturing to prescribe a bit of biological organization, which is probably an irreverent and is certainly an incautious thing to do. An improper reason for our desire to have sodium established in an exclusively extracellular position is that we have used this premise in obtaining measurements of extracellular fluid loss caused by processes of dehydration. This would mean that, if sodium is dependably extracellular, a loss of extracellular water can be easily computed from measurements of sodium loss from the body and of sodium concentration in the blood plasma. Direct measurement of water loss from the body is a complicated undertaking and moreover does not locate the loss.

This question of the position of sodium and of chloride ion is a very entertaining one because it requires the ingenuity of indirect approach. It cannot be dealt with directly by tissue analysis for the reason that we are unable to remove separately extracellular and intracellular fluid from a sample of tissue. If we beg the question and calculate the portion of the total water which is extracellular on the basis of the quantity of sodium or of chloride ion found in the sample, that is, if we assume that sodium and chloride are extracellular and that their concentrations are the same as found in accessible examples of extracellular fluid, we obtain values for extracellular water which seem quite reasonable and which suit our expectations for various tissues. For instance, in the case of muscle, which is a compact tissue, the value

found for extracellular water is about 15 per cent by weight, for a vascular tissue, such as liver, we find 30 per cent, and for the skin, the substructure of which is especially suitable for storage of interstitial water, we find a value of roughly 50 per cent. Darrow's value for extracellular fluid in the whole animal (the animal was a monkey), derived from measurement of chloride ion, is 20 per cent of body weight. There are many other items of evidence derived from various

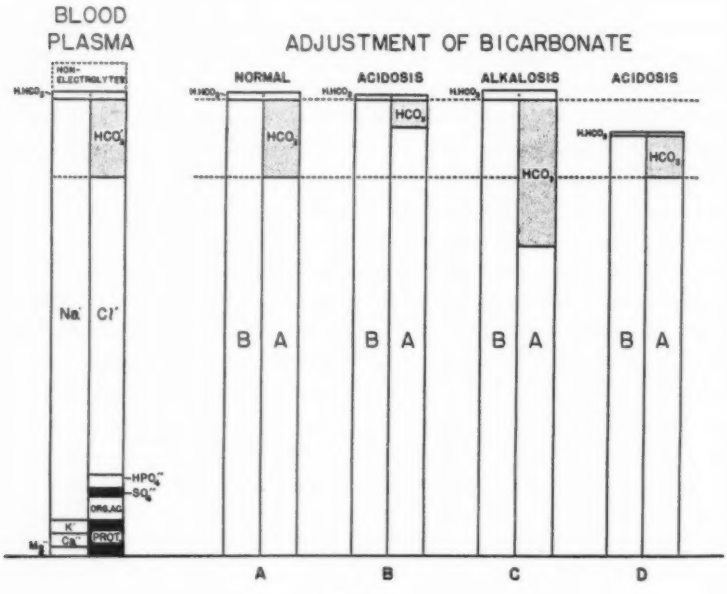


FIG. 3

methods of approach which indicate that sodium and chloride ion do not pass the cell barrier. I cannot here take the time to present them. Peters has put them together very skillfully and almost convincingly in his fine book on Body Water (2).

I wish now to try to describe, with the help of the diagrams in figure 3, the particular relationship of sodium and chloride ion to the reaction, in terms of hydrogen ion concentration, and to the osmotic value of extracellular fluid. In order to arrive at the few points

which I wish to make, I shall have to review a number of facts with which you are very familiar. The two immediate factors of control of hydrogen ion concentration in extracellular fluid are the concentrations of free carbonic acid and of the plasma bicarbonate. The latter is represented in the diagrams by the concentration of bicarbonate ion ($—HCO_3$) together with the fixed base which it covers. Hydrogen ion concentration is determined by the ratio of the values for these two factors. The ratio which produces the physiologically correct hydrogen ion concentration, which is described as pH 7.4, is one part of carbonic acid to twenty parts of bicarbonate. Under normal circumstances this ratio is provided by the presence in the plasma of 3 volumes per cent CO_2 as free carbonic acid and 60 volumes per cent as bicarbonate. The steadiness of reaction depends, then, on the accuracy of the mechanisms which sustain these values. The concentration of free carbonic acid is controlled by the respiratory mechanism. That is, the quantity of carbon dioxide dissolved in the plasma as carbonic acid rests upon the tension of carbon dioxide established in the residual air in the lungs to which the plasma is exposed as it passes through the alveolar capillaries. So excellent is this respiratory control that we almost never encounter an abnormality of reaction which is due to an incorrect concentration of free carbonic acid. The deviations from the normal value for hydrogen ion concentration which we describe as acidosis or alkalosis are therefore practically always caused by change in the other factor of control, the concentration of bicarbonate ion. The change in bicarbonate ion is, however, never a primary event. It is always the result of change in some other part, or parts, of the electrolyte structure. For instance, if the sum of the other acid radicals is by some cause increased above its usual value (diagram B), an equivalent quantity of bicarbonate ion will be dispossessed of base and released as free carbonic acid, a process which permits the covering of these radicals of strong acids. On the other hand, a reduction of this value exposes an equivalence of fixed base which is immediately covered by bicarbonate ion derived from the concentration of free carbonic acid which the respiratory mechanism sustains (diagram C), and in diagram D we see that a reduction of fixed base removes an equivalence of bicarbonate ion. In other words, the plasma bicarbonate value is determined simply by

the extent to which fixed base stands above the sum of the concentrations of the other acid radicals. Owing to this mendicant position of bicarbonate ion, its normal value depends on an integrity of the entire electrolyte structure, and here we can easily see the relatively very great importance of an accurate control of the two largest parts of this structure, sodium and chloride ion. An increase, for instance, of 50 per cent in the concentration of phosphate ion would cause a not very appreciable reduction of bicarbonate, whereas an increase to this extent of the chloride ion concentration would obliterate bicarbonate.

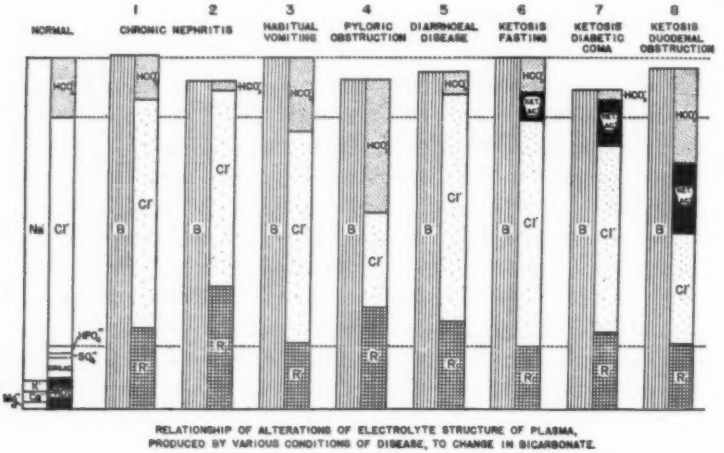
Now, as regards the osmotic value of extracellular fluid; this is of course determined by the sum of the concentrations of all of its chemical components. Here the concentration of sodium, owing to its large size and also to the adjustability of ($-HCO_3$), which we have just considered, plays an almost determining rôle. That is, the adjustable factor being on the acid side, it follows that the total base value determines the height of the diagram or, in other words, the total osmotic value of the electrolytes. The contribution of the non-electrolytes to the total osmotic value is relatively small, and nearly all of the base is sodium. We thus find that the osmotic value of extracellular fluid rests almost entirely on sodium. Chloride ion, the other large skeletal factor, plays no direct part in determining the osmotic value because of the circumstance that a change in the concentration of chloride ion will be offset by a reciprocal change in bicarbonate in the manner shown in the diagrams. Incidentally, these diagrams make it clear that the kidney must defend the total osmotic value of the plasma, regardless of plasma reaction. In other words, the kidney may not attempt direct restoration of the normal plasma bicarbonate, by retention or removal of base, for the obvious reason that this would disturb the osmotic value. And so, in the presence of severe alkalosis (diagram C), we are not surprised to find the kidney secreting an acid urine in order to defend the normal total base value in the plasma. The change in total base concentration which diagram D describes is never encountered in the presence of normal kidney function. To return to chloride ion, we may say that it does play an important structural rôle by filling in the space between a suitable bicarbonate concentration and the other relatively small anion values, and thus

permitting to the concentration of sodium a magnitude which enables it to almost determine the osmotic value.

Sodium having been assigned so much of responsibility for the structural integrity of extracellular fluid, it seems at least reasonable that it should have the assistance of an hormonal control, which the recent work on the adrenal cortical hormone suggests. The thought, however, may here be ventured that such a control might more appropriately relate to a fundamental property of extracellular fluid, its osmotic value, rather than to a single component of this value. Sodium being so dominating a component, this distinction would be difficult to establish.

To return now to the large changes in the bicarbonate concentration which a variety of disease conditions may cause (fig. 3). Obviously these changes disturb the carbonic acid: bicarbonate ratio upon which the normal value for hydrogen ion concentration depends. Change in the ratio is, however, of far less extent than would occur in an *in vitro* solution containing these buffer substances, because of adjustments by the respiratory mechanism. In the case of bicarbonate reduction (diagram B), the bicarbonate ion released as carbonic acid by the rise in the other acid values is immediately removed by way of the lungs and so is not added to the numerator of the ratio. Moreover, the respiratory mechanism undertakes to provide a lower than normal carbonic acid concentration, an adjustment which obviously tends to restore the normal ratio; and in the case of bicarbonate extension (diagram C), the carbonic acid concentration is appropriately raised. In the presence of considerable change in plasma bicarbonate, these adjustments of carbonic acid, roughly shown in the diagram, always fall somewhat short of complete restoration of the ratio, so that actual shift of reaction occurs; in the direction of acidity when bicarbonate is reduced and in the direction of alkalinity when bicarbonate is extended. The change in hydrogen ion concentration is, however, relatively minute as compared with a disastrous disturbance of reaction which is prevented by the change in bicarbonate. The increase in the quantity of the radicals of strong acids shown in diagram B is provided with base by recession of bicarbonate, and in diagram C an uncovering of strong base is prevented by extension of bicarbonate. So that we should regard these changes in the bicarbonate concentration, not as

plasma defects, but as beautifully alert adjustments in defense of reaction. Study of the pathogenesis of acidosis or of alkalosis therefore consists in finding the underlying defect in plasma structure which has made the change in bicarbonate necessary and in then explaining, if we can, the development of this defect in terms of the accompanying pathological circumstances. Theoretically, we are here commanded to do a complete dissection of the electrolyte anatomy of the plasma. This would be a laborious task and fortunately, in clinical studies, we are forbidden it because it would require an exorbitant blood sample.



RELATIONSHIP OF ALTERATIONS OF ELECTROLYTE STRUCTURE OF PLASMA, PRODUCED BY VARIOUS CONDITIONS OF DISEASE, TO CHANGE IN BICARBONATE.

FIG. 4

Also fortunately, we can usually obtain a fairly satisfactory explanation of the bicarbonate change by making only three measurements. The total fixed base value, the sum of individual values of the four cations, can be measured in a single procedure by the ingenious method of Fiske. If we then measure bicarbonate and chloride, there remain unmeasured only the four relatively small acid values at the bottom of the acid column. If we subtract the sum of the concentrations found for bicarbonate and chloride from the value obtained for total base, we have a remainder which measures these smaller anion values taken together. In the diagrams in figure 4, the value thus found is designated R.

These diagrams constructed from measurements obtained from patients will serve to illustrate the several types of plasma defect which various conditions of disease may cause, and the resultant change in bicarbonate. There are three possible processes of structural change; over-retention of materials, loss of materials, and introduction of abnormal materials. Over-retention of materials is referable to error in renal control which most often consists in failure to preserve the relatively very small values for the concentrations of phosphate, sulfate, and the radicals of the organic acids. There is thus produced the extension of R seen in diagram 1 which causes an equivalent reduction of bicarbonate. This we find not only in chronic nephritis, where we would expect to find it, but also, as may be seen in diagrams 4, 5, and 7, in situations which cause severe dehydration. These extensions of R indicate a secondary impairment of renal function, presumably from the inadequate volume flow of blood through the kidney which results when dehydration has progressed to the stage of reduction of blood plasma volume.

Loss of extracellular fluid materials is most frequently the result of failure of reabsorption of gastrointestinal secretions caused by continued vomiting or diarrhoea. These secretions are constructed from water and electrolytes, chiefly sodium and chloride ion, taken from the blood plasma, and which under normal circumstances are eventually returned to the plasma. The loss of plasma base, because of its direct relationship with the osmotic value, is accompanied by a corresponding loss of extracellular water. That is, the kidney, so long as it is able to operate accurately, regulates water removal in terms of base loss with the result that, as may be seen in diagram 3, the normal total base value is sustained. Measurement of the concentration of total base in the plasma therefore gives no information regarding loss of base. In the late stage of dehydration, however, inaccuracy of control of the total base concentration is nearly always found. As shown in diagrams 4, 5, and 7, the change is usually in the direction of reduction which, as revealed by measurements of the components of total base, is at the expense of sodium. This error of control is reasonably referable to the impairment of renal function which dehydration eventually produces. It is of interest to note that, in the case of the largest factor of the electrolyte structure, we find a failure of support in contrast with the over-retention of the small com-

ponents which produces the extension of R. This reduction of base and extension of R is also seen in diagram 2, which describes the severe acidosis which often develops in the terminal stage of chronic nephritis. Obviously we should discard the habit of thinking of renal disability only in terms of over-retention. The largest defect which may be found in the plasma structure is caused by the loss of chloride ion, in excess of the loss of sodium, in vomited stomach secretions. For instance, in diagram 4 we find that nearly two-thirds of the normal chloride ion concentration has been removed, making necessary an enormous extension of bicarbonate. In diagram 5 we find no recession of chloride ion, for the reason that loss of intestinal secretions withdraws rather more of base than of chloride ion. The acidosis in the case of this infant suffering from diarrhoeal disease is caused by the two structural changes—reduction of base and extension of R, which are referable to the eventual impairment of renal function by the process of dehydration.

The ketone acids constitute an abnormal factor in the electrolyte structure and the space which they use is always space which would otherwise be occupied by bicarbonate. In the simple situation described by diagram 6 there is no change in the other parts of the plasma structure. In the next diagram we find two other changes which have contributed to the bicarbonate reduction, a fall in the concentration of base and an increase in R. These changes are again the result of renal disability, caused by the severe dehydration which is always a prominent and a very dangerous feature of the situation in diabetic coma. The last diagram describes a not unusual combination of defects. We find in the case of a child with upper intestinal obstruction an extensive loss of chloride from vomiting and the presence of ketone acids from starvation. Chloride ion recession being larger than the accumulation of ketone acids, bicarbonate is necessarily extended, so that we have alkalosis in the presence of ketosis. This diagram should remind us that, although ketosis is the most frequent cause of acidosis, we cannot dependably infer bicarbonate reduction in the plasma from finding ketone acids in the urine.

I do not wish you to regard the defects which these diagrams describe as more than approximately representative of these several conditions of disease. A great variety of defects has been described

by Peters in nephritis and by Hartmann in diarrhoeal disease (3) (4). The chief purpose of the diagrams is to bring into view the relationship of various plasma defects to bicarbonate change.

In discussing these diagrams we have incidentally noted that extensive structural change in extracellular fluid is often accompanied by the volume change in the direction of reduction which we call dehydration. Leaving aside renal disease, this is almost always the case. And we may as well mention here that the patient usually is in far more imminent danger from the dehydration than from the acidosis or the alkalosis.

I shall try now to describe briefly the process of dehydration as caused by severe disturbances of gastro-intestinal function. There are of course other causes of dehydration, such as water deprivation,

TABLE 1

Approximate 24-hour quantities of digestive secretions

	cc.
Saliva	1500
Gastric secretions	2500
Bile	500
Pancreatic juice	700
Secretion of intestinal mucosa	3000
	8200
Blood plasma volume	3500

excessive sweating, diabetes and diabetes insipidus, but the cause which is clinically most prominent, particularly in pediatrics is, as we have mentioned, the continued wastage of gastro-intestinal secretions by vomiting or diarrhoea, which produces a progressive withdrawal of water and electrolytes from the blood plasma. The data in table 1 are shown to persuade you that this is a quantitatively adequate explanation. These estimates for the daily production of the several gastro-intestinal secretions by an adult add up to the rather startling total of 8 litres, a value more then twice as large as that of blood plasma volume. The diagrams in figure 5 describe the electrolyte composition of the gastro-intestinal secretions, and we see that they contain the structural components of extracellular fluid in differing patterns but at approximately the same total osmotic level.

Table 2 presents experimentally obtained data which will serve to describe the extent and also the rapidity of the loss of water and materials from the vascular compartment when reabsorption of gastric secretions is prevented (5). The experiment consisted in obstructing the pylorus of a rabbit by ligature and then sacrificing the animal near the end of the survival period, which was usually less than 48 hours,

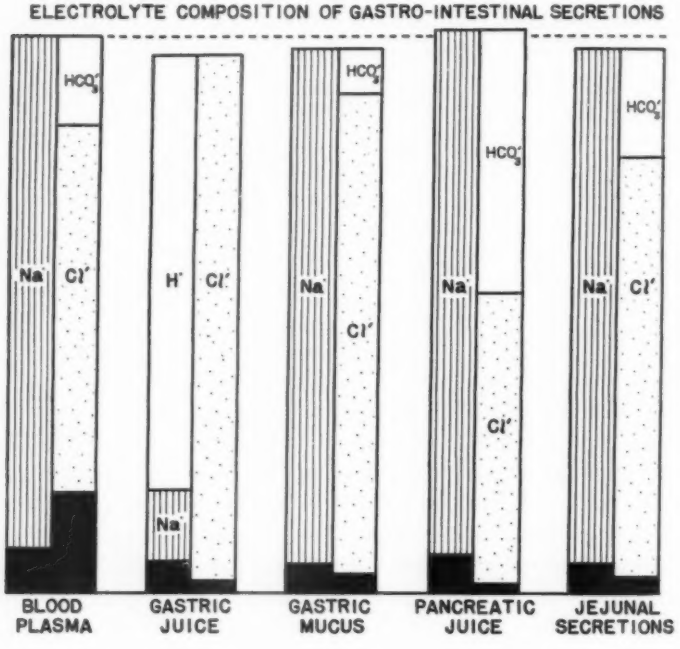


FIG. 5

and measuring the quantities of water, of fixed base, and of chloride ion found in the stomach. Since rabbits do not vomit and since there is no reabsorption from the stomach, the gastric secretions produced following the obstruction were thus accurately collected. The table also presents estimates of the total quantities of water, base and chloride in the vascular compartment at the outset of the experiment, derived from standard blood plasma data for rabbits. We note that

fixed base has entered the stomach to the extent of twice the total plasma quantity and, in the case of chloride ion, we find a loss of more than three times the plasma quantity. This greater withdrawal of chloride ion than of base explains the extension of bicarbonate found in blood plasma when stomach secretions are lost, which we have seen in a preceding diagram. The quantity of water found in the stomach is about two and one-half times the volume of the blood plasma. This water loss describes the extent to which interstitial fluid has been drawn into the vascular compartment in support of blood plasma volume. The volume of interstitial fluid, according to available evidence, is about three times the volume of the plasma (fig. 1), so that, under the circumstances of this experiment, we find that this reserve has been almost exhausted in the course of about thirty-six hours.

TABLE 2

Losses of water, fixed base, and chloride ion in gastric secretions following pyloric obstruction—(data from rabbits)

	cc.
Water lost	203 cc.
Initial plasma volume	83 cc.
Fixed base lost	270 cc. 0.1 N
Initial plasma fixed base	140 cc. 0.1 N
Chloride ion lost	309 cc. 0.1 N
Initial plasma chloride ion	85 cc. 0.1 N

Average of values found in four experiments.

In this experiment only gastric secretions are lost. We can therefore appreciate the extremely dangerous situation of an infant with diarrhoeal disease, who is losing not only gastric secretions but also the intestinal secretions.

The results of an experiment which illustrates the excellence of the defense of the blood plasma by interstitial fluid up to the point of exhaustion of this reserve are shown in figure 6 (6). Dehydration was produced gradually in a dog by draining away one of the gastro-intestinal secretions, the external secretion of the pancreas, by means of a fistula. Sodium has the same structural prominence and significance in pancreatic juice that it has in the blood plasma (fig. 5). Loss of this secretion will therefore remove along with sodium, in terms of its concentration, a corresponding quantity of extracellular water,

provided there is no replacement of sodium from the food intake. To avoid this, the dog was fed minced and repeatedly washed meat which contained almost no sodium. Water intake was not restricted. Dehydration due to the continued withdrawal of sodium is shown by the

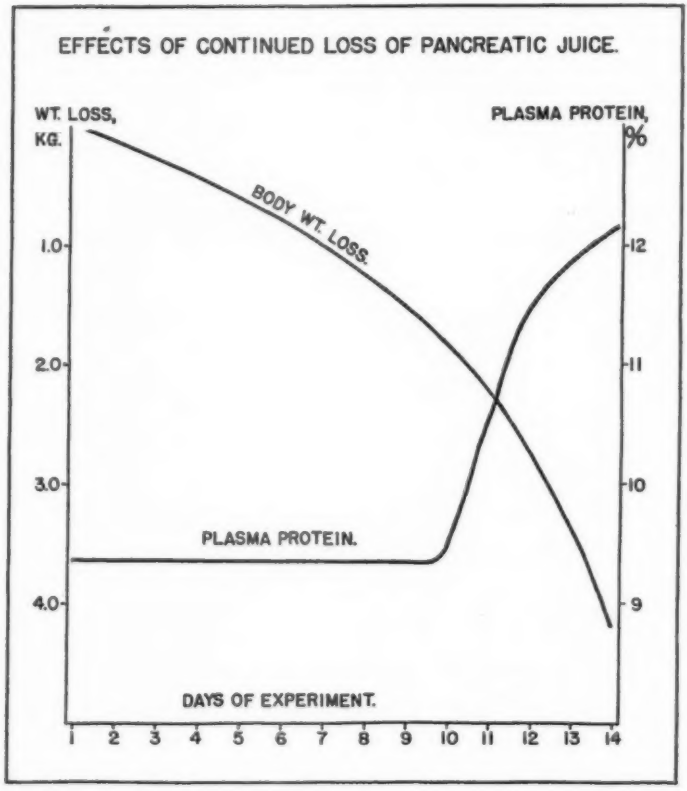


FIG. 6

progressive loss of body weight which, you will note, began at the outset of the experiment. The other curve is constructed from a series of measurements of plasma protein concentration taken as an index of plasma volume. There was, according to the plasma protein,

no change in plasma volume over the first ten days of the survival period, then presumably corresponding with exhaustion of the interstitial reservoir, we have a sharp and extensive rise indicating a rapid fall in the volume of the blood plasma. Over this ten-day period the dog ate well and was in excellent spirits. Four days later he was dead from dehydration. Measurements of other plasma values were made and they were all on the mark until plasma volume began to fall. Then there was rapid development of structural defects which together produced an extremely severe acidosis. The excellence of this protracted defense of the plasma has one disadvantage. It has defeated all of our attempts to discover the early stages of dehydration by examination of the plasma. These two curves describe very well the course of events in the case, for instance, of an infant with diar-

TABLE 3

Losses of extracellular and of intracellular fluid from an infant with diarrhoeal disease, calculated from total excretion of sodium, potassium and nitrogen in urine and stools

24-hour values

	cc.
Extracellular fluid loss calculated from Na	62
Intracellular fluid loss calculated from K	105
Intracellular fluid loss calculated from N	26
Intracellular fluid withdrawn from tissues	79

rhoeal disease, who is gradually dehydrating from incomplete reabsorption of gastric and intestinal secretions. Over a long period there are no symptoms other than those of the gastro-intestinal disturbance; then with alarming rapidity the evidences of failure of the functions of the blood, caused by the eventual reduction of plasma volume, begin to appear.

An obvious next question is whether or not the process of dehydration is limited to withdrawal of extracellular fluid (fig. 1). In other words, does the volume of intracellular fluid remain secure and undisturbed, at least until the interstitial reserve of fluid is exhausted or nearly so. We have attempted to study this question by using a measurement of loss of potassium from the body as evidence of, and as a means of estimating the extent of, a withdrawal of intracellular fluid. The suitability of potassium for this purpose may be seen by referring

to the last diagram in figure 2. The data in table 3 were derived from total excretion values for sodium, potassium, and nitrogen by an infant with diarrhoeal disease over a 24-hour period directly following admission to the hospital (7). Since the infant was so severely sick that food could not be given, these excretion values describe losses from the body. We find a withdrawal of extracellular fluid, calculated from the sodium loss, of 62 cc., and of intracellular fluid, estimated from the potassium excretion, of 105 cc. Here, however, we must consider the circumstance that the infant was fasting and obliged to consume body protein. Presumably the constituent water of protoplasm is released when protoplasm is consumed. The quantity of water so released was calculated from a measurement of the nitrogen excretion, and found to account for only one-quarter of the intracellular fluid loss estimated from potassium, and so we have the inference that the remainder, 79 cc., was withdrawn from intact protoplasm. Loeb, Atchley, Richards and Benedict have found similar evidence of loss of intracellular fluid in the dehydration of diabetes (8). It would seem likely that this loss of intracellular water is a late event in the process of dehydration, but we are not sure of this, and much more study will be required to define properly its relationship with the loss of extracellular fluid. It may well be that interstitial fluid cannot be withdrawn to any considerable extent without disturbing cell volume control. This is a disagreeable finding because it is difficult to see how anything can be done about it, in contrast with the admirably simple and effective means at hand for replacement of extracellular fluid. These we now have to consider with that hastiness which the position of therapy near the end of the lecture hour always seems to make necessary.

I shall only have time to consider those situations of such severity as to require immediate and energetic parenteral therapy, and I would remind you again that we nearly always encounter dehydration along with acidosis or alkalosis, and so are usually called upon to attempt to restore both the volume and the structure of extracellular fluid. Therapy is, nevertheless, astonishingly simple. Indeed, discussion of therapy consists largely in explaining how it is that plain isotonic sodium chloride solution will not only restore extracellular fluid volume but will also bring to pass the repair of a great variety of structural

defects. At first glance it would seem that a repair solution should be of the elaborate type used in perfusion experiments (fig. 7). Such a solution provides nearly all of the various parts of the electrolyte structure. It may, however, be expected that, with exception of the two extracellular ions, sodium and chloride, all of the other and smaller items of structure will be supplied by the processes of metabolism which carry on even in a situation of starvation. It therefore does

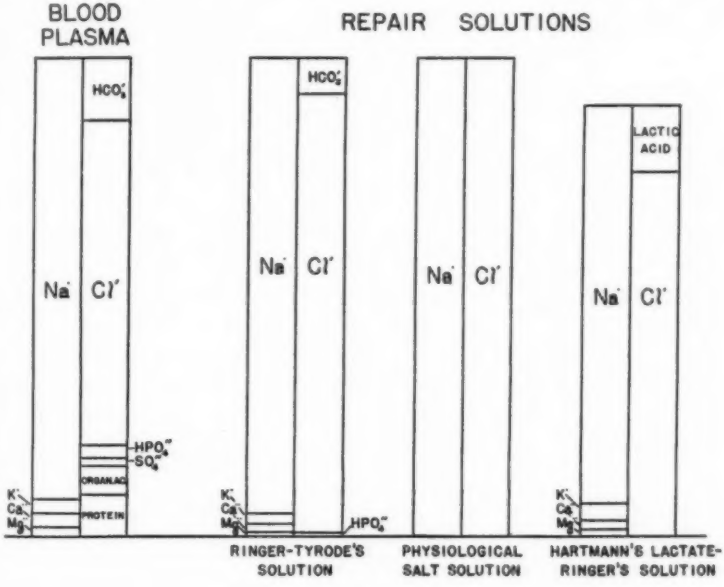


FIG. 7

not seem necessary to employ them in a repair solution. Now, obviously, salt solution supplies equal quantities of sodium and of chloride ion, and in the plasma there must be considerably less of chloride ion than of sodium in order to provide space for the important bicarbonate ion concentration. Here we ask the kidney to remove chloride ion from the administered salt solution to the extent which its prescribed concentration demands. Our expectation, then, when we supply water, sodium and chloride ion abundantly in the form of

salt solution, is that the kidney will so regulate the retention of these materials, and of the materials contributed by metabolic processes, that extracellular fluid volume will be restored and defects of structure repaired, with the result that the bicarbonate ion concentration will be permitted to resume its usual value. This expectation obviously requires an alert and capable kidney and we have noted that in advanced dehydration there is extensive impairment of renal function. A second and very important therapeutic requirement is, therefore, restoration of accuracy of renal control over the parts of plasma structure. The use of intravenous glucose solution rests chiefly on this premise. Glucose solution does in some way, usually quite rapidly, restore renal function, probably by reestablishing plasma volume and adequate volume flow of blood through the kidney. There is also the consideration that glucose solution supplies the kidney with water for removal and salt solution does not. At least theoretically, until volume has been restored, the water which the isotonic salt solution provides should be retained. Glucose solution, since the glucose is soon oxidized, constitutes a surplus of water to be removed by the kidney, which presumably facilitates an accurate construction of urine. And there is of course another important service that glucose provides, namely; that it will demolish an accumulation of ketone acids, if there is this blemish in the plasma structure, as there so often is, and which is the only plasma defect which salt solution cannot repair. We have then these two extremely simple therapeutic agents for the treatment of dehydration and accompanying acidosis or alkalosis. We will expect, however, that the process of reconstruction of extracellular fluid will require an appreciable interval of time, although it is usually well under way within six or eight hours. So that, when there is severe acidosis, it is wise to repair the plasma bicarbonate directly at the outset of treatment. This can be done by intravenous injection of a solution of sodium bicarbonate. A better procedure is to use, in place of salt solution, Hartmann's ingenious solution, the essential feature of which is that it contains sodium lactate along with sodium chloride. The lactic acid radical is oxidized after absorption and bicarbonate ion takes its place. The alkalinity of a repair solution containing bicarbonate, which is undesirable if it is to be given subcutaneously, is thus avoided. Hart-

mann's solution also contains other probably gratuitous condiments and is a bit hypotonic. We have preferred to use simply a mixture of one part isotonic sodium lactate solution to five parts isotonic salt solution. Such a lactate-salt solution is a logical agent for the treat-

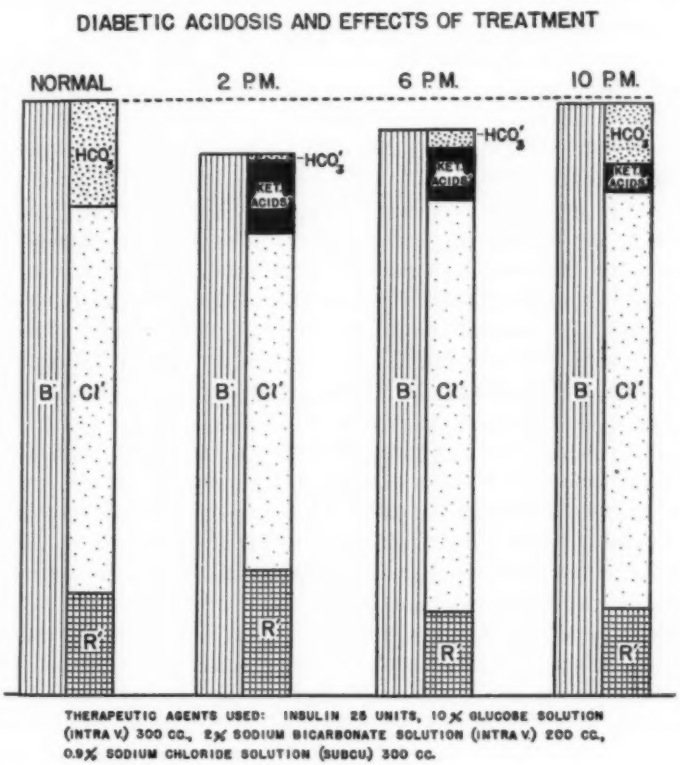

DIABETIC ACIDOSIS AND EFFECTS OF TREATMENT
NORMAL
2 P.M.
6 P.M.
10 P.M.
HCO'3
KETO ACIDS
B'
Cl'
R'
THERAPEUTIC AGENTS USED: INSULIN 25 UNITS, 10% GLUCOSE SOLUTION (INTRA V.) 300 CC., 2% SODIUM BICARBONATE SOLUTION (INTRA V.) 200 CC., 0.9% SODIUM CHLORIDE SOLUTION (SUBCU.) 300 CC.

FIG. 8

ment of dehydration accompanied by severe acidosis. If the acidosis is not of severe degree, salt solution does as well, and salt solution is of course the agent of choice in the presence of alkalosis.

The means at hand for replacement of the internal environment are thus extremely simple and practicable and are often quite dramatically

life saving. The diagrams in figure 8 will serve to illustrate the rapidity of their effectiveness. The patient was a three-year-old child in diabetic coma, extremely dehydrated and with only a very small remnant of plasma bicarbonate. As shown by the diagrams, an almost complete repair of plasma structure was obtained in the course of eight hours.

In this brief consideration of extracellular fluid disturbances, I have wished particularly to emphasize the intermingling of volume and structural change. Since both defects are reparable by the same agents, there is little practical validity for the separate contemplation of dehydration and acidosis or alkalosis. Dehydration being the more dangerous event and requiring a larger quantity of the repair materials, its correction may be taken as the objective of treatment. If completely attained, the accompanying acidosis or alkalosis will have been incidentally removed. I have also wished to make clear the prominence of secondary renal disability and the importance of restoring accuracy of kidney function upon which the correct utilization of the repair materials depends. These considerations produce two items of therapeutic rational; we depend on salt solution for the restoration of the volume of extracellular fluid and the repair of all defects of structure except the defect caused by the presence of ketone acids, and on glucose solution to enable the kidney to correctly control the materials supplied by salt solution and for the oxidation of ketone acids. It is important that these explicit indications for the use of these two solutions be separately obeyed. Particularly to be avoided is the error of expecting replacement of a loss of extracellular fluid by glucose solution. Dehydration can be repaired only by salt solution. In situations of any considerable degree of severity the use of both solutions is almost invariably indicated. When there is acidosis of such dangerous degree that it is unwise to await the reparative effects of these two agents, immediate support of the plasma bicarbonate by the intravenous administration of a solution of sodium bicarbonate or a solution containing sodium lactate is indicated. It should be remembered that this is an additional procedure which does not replace the requirement for an energetic use of salt solution and glucose solution, on which we must depend for the reestablishment of extra-

cellular fluid on the physiologically correct basis of an accurately functioning mechanism of control.

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EXTRACELLULAR FLUID

Renal Defense of Extracellular Fluid: Control of Acid-Base Excretion and the Factors of Water Expenditure*

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From The Department of Pediatrics, Harvard University Medical School

The preceding lecture offered a brief and, in many respects, an incomplete description of the chemically very ingenious fluid which provides the organism with an immediate environment in which physico-chemical properties are held at nearly stationary values. Obviously this fluid is constructed from materials derived from the food and water intake. As regards control of these materials; except for the concentration of free carbonic acid which is held at a fixed value by the respiratory mechanism, and the concentration of protein which is established by a mechanism which is not yet visible, the chemical pattern of the blood plasma, and of the interstitial fluid behind the plasma, is sustained by the kidney. The kidney is very inadequately described as an organ of excretion. Were the removal of waste products its only function, a much simpler mechanism would suffice. Its complexity of design and intricacy of function are required for the construction and accurate defense of extracellular fluid on the chemical constancy of which depends the successful operation of intracellular processes. Macallum (*loc. cit.*), regarding the establishment of the enclosed aqueous medium as the largest forward step in the history of the animal organism, has described the kidney as the organ par excellence of evolution.

The recent splendid advances in renal physiology make it clear that control of the composition of the plasma rests chiefly on a process of selective reabsorption of water and materials from glomerular filtrate. The mechanisms of this remarkable process, which sustain the

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various parts of the plasma structure at their prescribed values and manage a situation of wide osmotic unbalance between plasma and tubule fluid, have not as yet been uncovered to any appreciable extent, and I am not competent to offer you even surmise in this fascinating direction of inquiry. What I shall try to describe are certain adjustments of the composition of the urine in terms of acid-base equivalence which are necessary in order that the process of selective reabsorption may successfully defend the electrolyte structure of the plasma. The requirement for these adjustments results from the circumstance that widely unequal quantities of base and acid must be removed from the plasma. For instance, the total quantity of acid radicals which derives from a usual diet is greatly in excess of the intake of fixed base. Obviously then, if these acid radicals which, while being conveyed in the plasma, must be covered by fixed base, were permitted to carry their equivalence of fixed base into the urine, plasma base would be rapidly depleted. On the other hand, if the excess of acid radicals were permitted to enter the urine uncovered, a devastating degree of urine acidity would result. Not infrequently the situation is reversed and the kidney must remove a larger quantity of fixed base than of the acid radicals. So, there is obvious need of defensive adjustments which will permit the construction of urine within the physiological bounds which have been set for the reaction of urine.

I shall review these adjustments briefly and then show you quantitative data which display them in operation in several situations of acid-base metabolism. We might first consider the usual situation, which requires the removal in urine of acid radicals in excess of fixed base. The relative amounts of the four acid radicals and of the four components of fixed base which derive from an ordinary food intake are shown by the diagrams in figure 1. The quantity of fixed base (diagram B) is seen to be not much more than half as large as the total acid excretion in terms of base equivalence at the reaction of blood plasma (diagram A). As Lawrence Henderson has shown us, there are two factors of adjustment which manage the removal of this large excess of acid. One of them rests on the ability of the kidney to secrete a solution of materials which is more acid than the blood plasma. The limit of urine acidity is about pH 4.8. This is the reaction of a solution of monobasic phosphate. Since the radical

of phosphoric acid is conveyed in extracellular fluid almost entirely as dibasic phosphate (fig. 7), there is here opportunity for the kidney to accomplish the removal of HPO_4 with an expenditure of only a little more than half the base which covers it in blood plasma. Also, the organic acids produced by metabolism, being weakly acid substances, may be present in acid urine, uncovered by base, to the extent of an appreciable proportion, 10 to 20 per cent, of their total value. So that in removing these two of the four acid radicals from the plasma

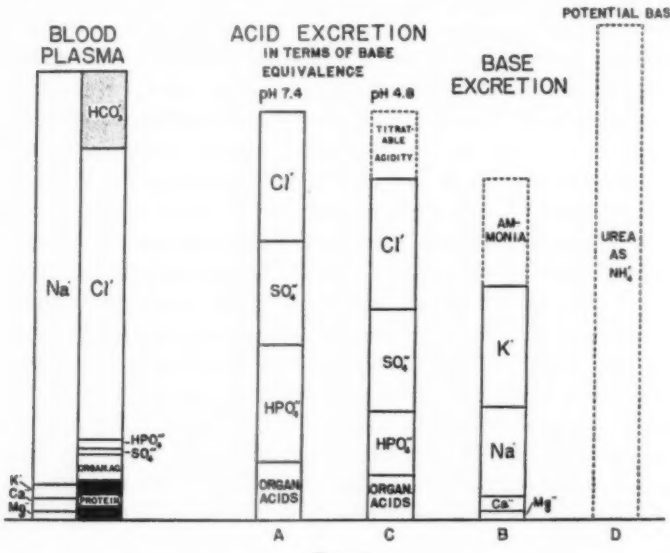


FIG. 1

an economy of base is possible. The other two factors of the acid excretion being the radicals of extremely strong acids must be provided with their full equivalence of base. The presence of even minute quantities of hydrochloric or of sulfuric acid would produce an hydrogen concentration far beyond the limit set for urine. The extent of the reduction of the base equivalence of phosphoric acid and of the organic acids in urine secreted at pH 4.8 is shown in diagram C, and at the top of the column we see the size of the saving of base thus obtained. This, as Henderson pointed out, can be easily measured

by titrating the urine with standard alkali back to the reaction of the blood plasma. This economy of base covers only a part of the discrepancy between the total acid excretion in terms of its plasma base equivalence and available fixed base. The other and larger factor of adjustment, which completes the covering of the acid excretion, is a regulated production of the base ammonia from the neutral end product of metabolism urea. It is an important premise of acid-base

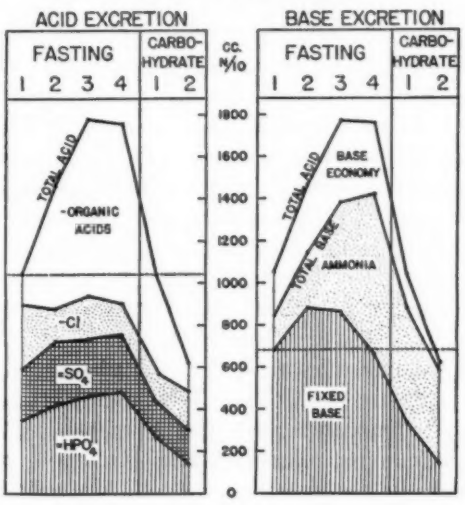


FIG. 2

metabolism that ammonia cannot be used in acid-base adjustments within the organism. Base, at least in terms of the gross anatomy of acid-base metabolism, has to be entirely fixed base. Curiously, any appreciable concentration of ammonia in body fluids exerts a toxic effect, but ammonia can be used for the covering of acid radicals as they enter the urine, and here it plays an extremely important rôle in defense of the fixed base content of extracellular fluid. The abundant availability of ammonia is shown by diagram D which describes the urea concentration in terms of ammonia.

Control of the use of fixed base in the process of acid excretion to the extent necessary to maintain the fixed base of extracellular fluid is, then, accomplished by the operation together of these two adjustments: an absolute saving of base determined by the degree of urine acidity and a regulated substitution of ammonia for fixed base. The data presented by means of the diagrams in figure 2 will serve to illustrate this control (1). These measurements were obtained from consecutive twenty-four hour urine specimens collected over a period of four days of fasting followed by a two-day period in which the only food given was a small amount of cane sugar. The subject was an epileptic boy who was fasted as a therapeutic measure. The basic and acid radicals of the usual type which present for excretion during fasting derive from consumption of body protoplasm. In addition, owing to the low level of carbohydrate metabolism, a large quantity of incompletely oxidized fatty acids must be conveyed into the urine. The administration of a small amount of carbohydrate removes this ketosis and also, by its protein-sparing effect, reduces the quantity of other acid radicals and of fixed base released for excretion. These circumstances produce a wide range of change in the factors of acid-base excretion and thereby extensively exercise the regulatory mechanism which guards the fixed base level in the blood plasma.

In the left-hand diagram, the individual values found for the four acid radicals, expressed in terms of their base equivalence at the reaction of blood plasma, are superimposed so that the top line measures the total acid excretion. The right-hand diagram is constructed by laying off again the line measuring the total acid excretion and then plotting downwards from it the values found by titrating the urine to the reaction of blood plasma. The size of the base economy factor is thus defined and a line produced which measures the total base excretion. From this line the measurements of the quantities of ammonia found are laid off downward and leave a remainder which defines the fixed base excretion. The two factors controlling the use of fixed base in the process of acid excretion are thus given quantitative description and we see that the acid radicals, which while being conveyed to the kidney must be completely covered by fixed base, are permitted to carry fixed base into the urine to the extent of only about one-half of their total equivalence. The alert adjustability of the

regulatory factors is evident in the diagram. Their control is here described in terms of the total fixed base excretion. This is an incomplete account of their service, which is to defend the individual requirements of the several components of extracellular fluid base, particularly of sodium because of its exclusively extracellular position. We will therefore expect to find that the fixed base permitted to enter the urine during fasting is composed almost entirely of potassium,

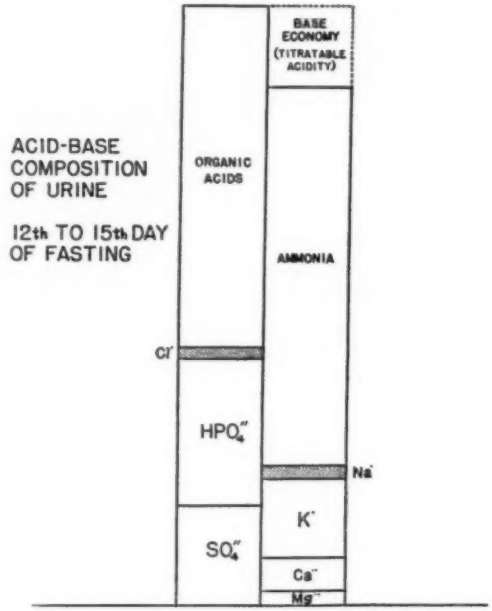


FIG. 3

calcium and magnesium, released by destruction of protoplasm. Figure 3 describes the composition of the acid-base excretion as found over the later part of a longer fast undergone by another subject. Here we find that sodium is a small factor in the fixed base excretion and we may also note, on the acid side of the diagram, a corresponding restraint of the excretion of the other important factor of extracellular fluid structure, chloride ion. It may well be that the presence of these

small quantities of sodium and chloride ion represent an appropriate reduction of extracellular fluid volume along with the decrease of total protoplasmic mass caused by fasting, rather than imperfect conservation.

We may now consider the reverse situation in which an excess of

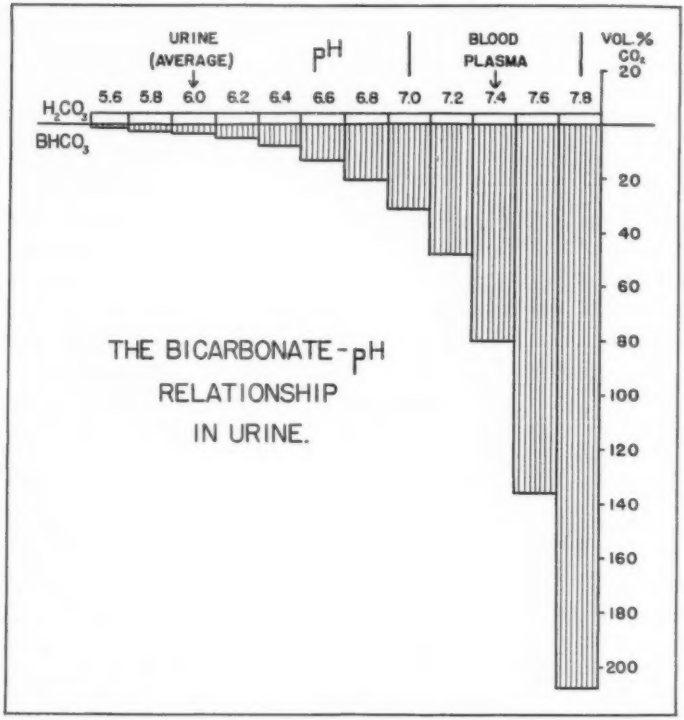


FIG. 4

fixed base over acid claims removal in the urine. Obviously what is needed here is an acid analogue of ammonia; that is, an acid substance which is abundantly at hand and can be placed controllably in the urine. Carbonic acid suits these specifications ideally. Its availability is practically unlimited. Routinely it leaves the body base

free by way of the lungs, but when needed can, to a regulated extent, be deflected into the urine.

Study of the concentrations of carbonic acid and of bicarbonate in urine reveals an interesting relationship (2, 3, 4). We find that the concentration of carbonic acid in urine has a nearly stationary value of about the same magnitude that is found in the blood plasma (fig. 4). Carbonic acid is unique in this respect. All of the other components of urine are found at widely varying concentrations which are usually far above their blood plasma levels. Apparently the concentration of carbonic acid in urine rests, as does its blood plasma value, on the carbon dioxide tension in the residual air of the lungs; so that we might venture to say that carbonic acid is not secreted by the kidney but simply diffuses into the urine. Since hydrogen ion concentration is determined by the ratio of the concentrations of free carbonic acid and bicarbonate, this fixed value for the numerator of the ratio prescribes the individual values for bicarbonate concentration over the range of urine reaction, and you will note that as reaction moves in the direction of alkalinity the bicarbonate values rapidly become very large. So that we have here a simple and excellent mechanism for the removal in urine of fixed base in excess of acid. The extra base is removed as bicarbonate and, starting at the reaction of blood plasma, progressively enormous quantities of base as bicarbonate may be placed in the urine within a very small range of reaction change. This mechanism, which rests on the persistent presence of free carbonic acid, provides a very efficient defense of the alkaline bound of urine. Actually tested by ingesting large amounts of alkali, it is found to be almost impossible to push the reaction of urine beyond pH 7.8. Haldane, I think, holds the record in this research. He once ingested ninety grams of sodium bicarbonate at a single sitting. He explains that this can only be done directly after a massive English breakfast. He achieved, as I remember it, a pH of 7.9.

Experimentally obtained data which will serve to illustrate the removal of fixed base as bicarbonate in defense of the anion components of the plasma, particularly of chloride ion, are presented in figure 5. The experiment consisted in obstructing the pylorus of a dog (5). Then, after permitting dehydration caused by loss of stomach secretions to proceed for two days, large quantities of salt solution were

given by intraperitoneal injection. Owing to the larger loss of chloride ion than of sodium in stomach secretions, the sodium deficit is replaced from the administered salt solution long before that for chloride ion. The kidney is then called upon to remove sodium but to continue to retain chloride ion. Measurements of the acid radicals in the urine, which was collected in consecutive twelve-hour specimens, are given in the left-hand diagram. The excretion of chloride ion remains at a small value throughout the experiment, indicating that the quantity of salt solution given was not enough to replace entirely

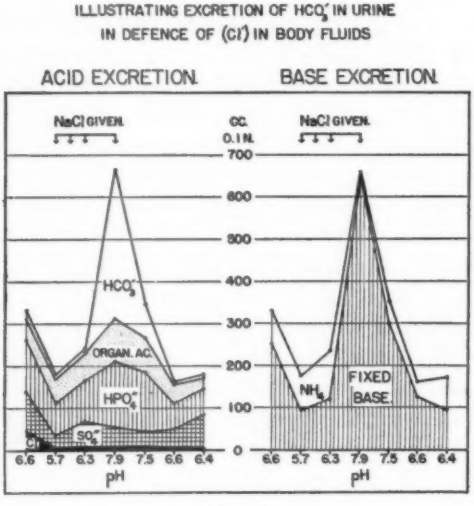


FIG. 5

the chloride ion loss. In the other diagram, following the third injection of salt solution, we find an extensive rise in fixed base excretion which represents removal of surplus sodium. In the diagram of the acid excretion, this is seen to be covered by a peak composed of bicarbonate ion. Incidentally it may be noted that, under the circumstances of this situation, the administration of a neutral salt has caused the secretion of an intensely alkaline urine, an event which clearly demonstrates the separate control of sodium and of chloride ion according to their individual retention requirements. It is, of

course, on this separate control that we depend when we provide salt solution for the repair of defects of the structure as well as of the volume of extracellular fluid.

I wish now to return to figure 4 in order to point out an item of interest in relation, not to the removal of excess fixed base, but to conservation of base which, we have noted is the usual requirement.

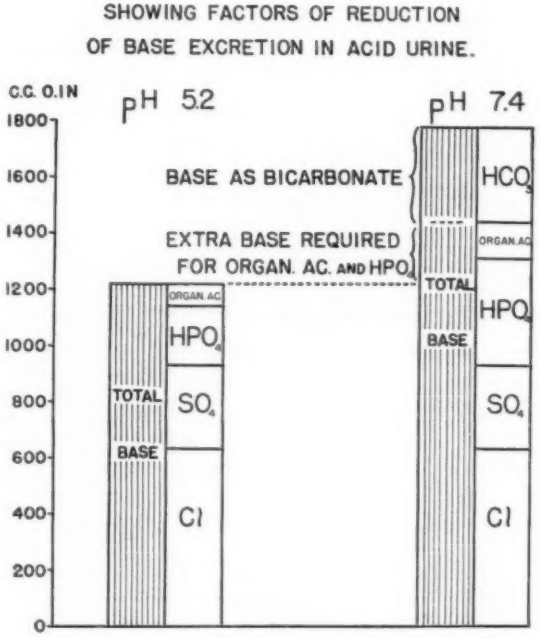


FIG. 6

In urine of the reaction of blood plasma we find a quite large quantity of base as bicarbonate. In urine of usual reaction, which is in the neighborhood of pH 6.0, we find only a small bit of base as bicarbonate. Now, since carbonic acid can be removed from the body base free by way of the lungs, base in the urine as bicarbonate, under circumstances demanding conservaton of base, must be regarded as base wasted. We can therefore recognize as a chief significance of the usual reaction

of urine, an avoidance of a useless expenditure of base as bicarbonate. We have here, then, another item of base conservation and it is perhaps of interest to compare it quantitatively with the saving of base accomplished by removal of the radicals of phosphoric acid and of the organic acids in acid urine which we have already considered. This comparison is provided by the diagrams in figure 6. The first diagram describes the acid-base composition found for a specimen of urine which

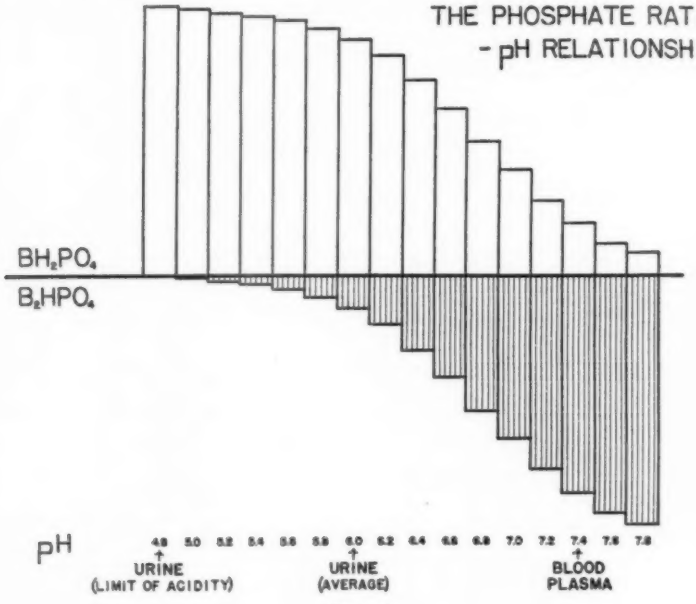


FIG. 7

was secreted at pH 5.2. The other diagram shows the much larger quantity of base which would have to be present if the same quantities of the acid radicals were removed in urine at the reaction of the blood plasma. Owing to extension of the base equivalence of phosphoric acid and of the organic acids, extra base would be required to the extent indicated and there would also be an even larger addition of base as bicarbonate.

These two items of base economy, and also the mechanism of removal of excess base which we have considered, make clear the great advantage to the kidney of being permitted to construct urine over a pH range of the width shown in figure 4. The movement of pH, as Sendroy, Seelig and Van Slyke have pointed out, can be explained very simply and probably correctly as a consequence of the operation of the process of selective reabsorption (4). At pH 7.4 we have the bicarbonate content of glomerular filtrate as it enters the tubules. If a larger quantity of the anions than of fixed base must be returned to the plasma, the fixed base left behind will be supplied with bicarbonate ion, derived from the sustained concentration of carbonic acid, with the result that bicarbonate will extend and pH will move in the direction of alkalinity. On the other hand, if there is requirement for a larger return of fixed base than of anions to the plasma, reabsorption of fixed base seen here as bicarbonate will cause the pH of urine to move toward its usual position. At the same time the process of absorption of one equivalence of fixed base from the dibasic phosphate of the filtrate is going on and the phosphate ratio is changing; in step, of course, with the change in the carbonic acid-bicarbonate ratio. The phosphate ratio behaves just as it would in an *in vitro* solution (fig. 7). The quantity of phosphate ion remains stationary and removal of fixed base simply converts dibasic phosphate into monobasic phosphate, so that the numerator of the ratio gains as the denominator diminishes, and in consequence there is less resistance to movement of pH than in the case of the ingeniously controlled carbonic acid-bicarbonate mechanism. Adequate admiration for this mechanism may be gained by noting in figure 8 the unsuitableness of ordinary unguided bicarbonate buffering. Here we find almost no defense of reaction on the alkaline side of glomerular filtrate. Very small increments of bicarbonate carry reaction rapidly in the direction of alkalinity. Also reaction would have to move considerably further in the direction of acidity to avoid loss of base as bicarbonate. Returning now to figure 4, we can appreciate the effectiveness of the device of the fixed numerator which, by producing a rapid increase in bicarbonate in the direction of alkalinity and rapid decrease in the other direction, enables the kidney to remove a widely variable quantity of fixed base within a short range of pH change. The buffer salts, however, do not

adequately defend the acid boundary of urine reaction. At pH 6.0 there is not much dibasic phosphate left (fig. 7) and bicarbonate is also almost exhausted (fig. 4). But by the time this degree of acidity is reached, the ammonia mechanism is well under way and, by supplying ammonia for the covering of acid radicals, releases fixed base for absorption to such further extent as maintenance of plasma base may require.

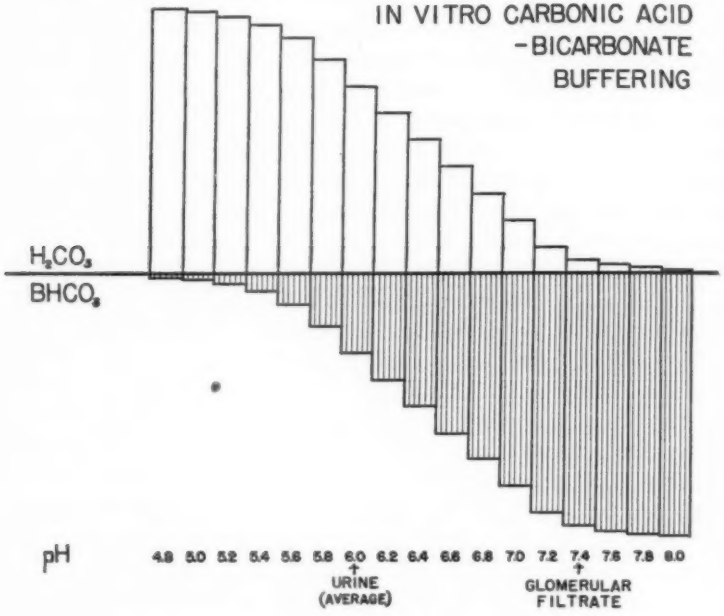
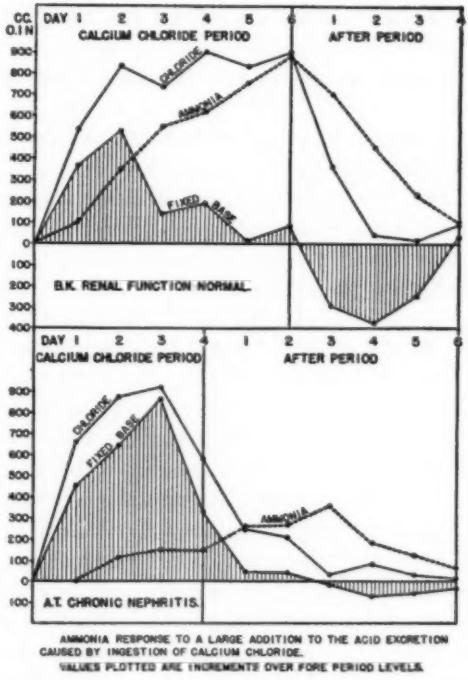


FIG. 8

We thus find these several alert and widely extensible mechanisms which permit the kidney to sustain the electrolyte pattern of extracellular fluid by casting into the urine unequal quantities of acid and fixed base. The automaticity of this defense of the physiological bounds of urine reaction is visible in the case of the buffering substances. The motivation of the beautifully regulated mechanism which supplies just the right quantity of ammonia is still hidden away.

It is now in order to ask what happens to these regulatory mechanisms in the presence of renal disease. Since the early work of Henderson and Palmer it has been known that there is a disability of the ammonia production mechanism in chronic nephritis. The data in figure 9, which were obtained in a study of the diuretic action of calcium chloride, will serve to illustrate this defect (6). Calcium



AMMONIA RESPONSE TO A LARGE ADDITION TO THE ACID EXCRETION CAUSED BY INGESTION OF CALCIUM CHLORIDE.
VALUES PLOTTED ARE INCREMENTS OVER FORE PERIOD LEVELS.

FIG. 9

chloride is in terms of acid-base metabolism an acid substance because relatively little of the calcium which it provides is absorbed from the gastro-intestinal tract, whereas nearly all of the chloride ion is absorbed and thus constitutes a large addition to the usual excess of acid over fixed base which presents for removal in urine. As we have just seen (fig. 7), the extent to which base can be saved by increasing

the acidity of urine beyond its usual value is almost negligible. Management of a large addition to the acid excretion therefore rests almost entirely on the ammonia mechanism, and to such extent as the extra acid is not covered by an increase in ammonia production, fixed base will be withdrawn from the body. The measurements recorded in figure 9 are of increments of chloride ion, ammonia and fixed base in the urine over fore period values, during a period of calcium chloride administration. They are presented simply to show the much slower response of ammonia in the case of the patient with chronic nephritis and, in consequence, the much larger withdrawal of fixed base.

So that there is in chronic nephritis, owing to this sluggishness of ammonia production, the hazard of fixed base depletion. Peters has presented evidence of fixed base deficit in chronic nephritis and has indicated the importance of guarding such patients against gradual dehydration by providing them with an adequate salt intake (7). The requirement is for sodium chloride. In other respects the rational of a low salt intake in chronic nephritis remains undisturbed. We have long had the habit of thinking of impairment of renal function in terms of over-retention of substances. Here, in the case of the most important structural component of extracellular fluid, we find that the error in control is usually in the other direction. This question of base deficit in nephritis deserves further study in order that we may have a better quantitative appraisement of it.

Diverging now from the acid-base aspect of kidney function, I will undertake to present briefly the results of several attempts during recent years to define an important dimension of the renal mechanism, namely; the quantity of water which has to be used in removing substances from extracellular fluid. Based on the preceding lecture, the statement may be ventured that only three materials are directly required for the maintenance of extracellular fluid; water, sodium and chloride ion, its many other components being supplied by the processes of metabolism. This is not the case for sodium and chloride ion because of their extracellular position, and it may be said that removal of water from the body occurs entirely at the expense of, and in terms of the transport function of, extracellular fluid. We can therefore understand why two special sensations were devised to

insure adequate maintenance of extracellular fluid; a specific craving for sodium chloride and the sensation of thirst.

The largest item of water expenditure is the water requirement of renal function. The story of the development of an economical use of water by the kidney as uncovered by E. K. Marshall and Homer Smith is, as you know, an extremely entertaining one. The glomerulus appears first in fresh water fishes and, by introducing the device of filtration, facilitates removal of an enormous excess of water over substances. Then, with the development of terrestrial forms, the requirement is reversed and an economical use of water becomes imperative, whereupon the loop of Henle is devised, and the kidney is enabled to reabsorb water in large excess over substances. And so, as the result of the invention of the glomerulus which so excellently suited the fresh water fishes, we are obliged to reabsorb more than ninety per cent of the water which passes through it. The history of the filtration reabsorption method of renal control thus describes an exciting and eventually successful escape from a misadventure in design.

Cushny, in formulating his modern theory of renal secretion, suggested that limitation of the return of water from glomerular filtrate to the plasma is determined simply by a certain level of osmotic pressure resistance which the process of reabsorption of water in excess of substances eventually produces. According to this explanation obligatory water expenditure would be the same for all of the substances removed in urine. But it was soon found that this is not the case for two prominent and easily studied substances, urea and sodium chloride. The so-called maximal concentration for urea in urine is found to be nearly twice that for sodium chloride.

In our attempts to define water expenditure by the kidney in terms of individual substances, we have used the very simple plan of feeding the substance to rats and measuring their concentrations in the urine (8). A large amount of the substance to be studied is placed in a maintenance diet of the purified type, and so constructed as to produce a minimum of other materials claiming excretion in the urine. It is not, of course, possible, by any device of experimentation, to arrange for the secretion of urine containing only one substance. In these studies, owing to the willingness of the rats to ingest huge amounts of

the substances, this goal was approached to the extent that the substance under study was found to constitute about eighty-five percent of the total of materials in the urine in terms of concentration. The rats were permitted to adjust their water intake as they thought best. This was a particular feature of the plan of experiment. We wished to study water expenditure under circumstances as nearly normal as possible. We therefore preferred concentration values in the urine which could be described as optimal rather than maximal.

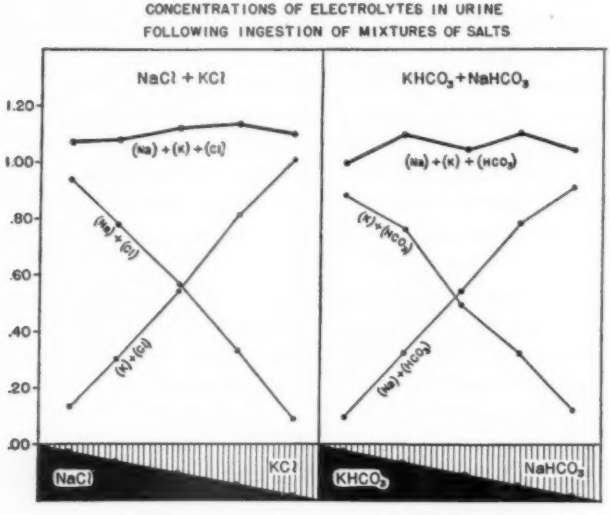


FIG. 10

Here we depended on the rats to accurately adjust their water intake in terms of the renal water requirement. Their coöperation in this respect was quite remarkable.

I wish first to show you the results of experiments in which several salts were fed separately and as mixtures at a stationary high level of intake (fig. 10). For instance, in the first of these two experiments, sodium chloride alone was placed in the diet, and then, in succeeding periods, was replaced in steps by potassium chloride. The object of the experiments was information regarding the individual water

requirements of the ionic components of these salts. The concentration values were obtained from twenty-four hour collections of urine. The chief finding from these experiments in which chlorides and bicarbonates of sodium and potassium were fed is easily legible in the diagrams, and consists in the fact that the sum of the concentrations of the components of these salts is a nearly stationary value. From

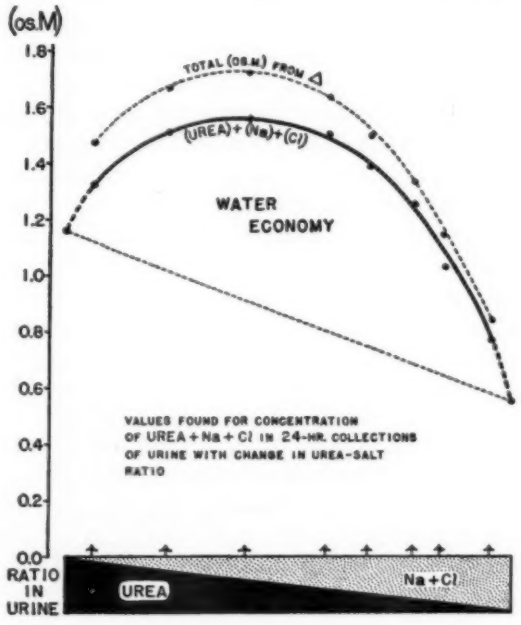


FIG. 11

this we may infer that their individual water requirements are the same and are directly additive. We obtained approximately the same result when mixtures of chlorides, phosphates and sulfates were fed. And so we find that, according to the evidence of these experiments, these various ions which, as parts of the electrolyte structure in extracellular fluid, are sustained at widely differing concentrations, are removed in urine on a basis of osmotic equality. The electrolytes

thus seem to obey Cushny's postulation of an identical and additive water requirement in terms of concentration.

We next studied the removal in urine of mixtures of salt and urea. Although their individual water requirements are known to be widely different, we expected to find them directly additive when the two substances are removed together. It was a great surprise to find that this is apparently not the case. Figure 11 describes the results of an experiment in which, over successive periods, the rats were fed at a very high level with first urea alone and then progressive replacements of urea by sodium chloride. The values found in the urine for the sum of the concentrations of urea and sodium plus chloride ion produce a curve. From this curve we have by projection a value for urea when alone in the urine and another much lower value for sodium chloride in the complete absence of urea. In other words, these two values may be taken as describing the separate water requirements of urea and of sodium chloride. If these requirements are additive when mixtures of the two substances are removed, it would be expected that, as urea is replaced in the urine by sodium chloride, the sum of the concentrations of the two substances should fall gradually along the path indicated by the broken line, because of the larger water requirement for the removal of sodium chloride. Instead we find the values for the sum of the concentrations on a curve which rises far above the expected values, indicating apparently that when urea and sodium chloride are removed together in urine their individual water requirements are much less than additive. Since concentration is the reciprocal of volume, the space between the expected and the found values represents a large economy of water. This finding was published as indicating a hidden water saving device, the mechanism of which would probably be eventually found to rest on the unique physical properties of urea. Recently, the results of further study have suggested a more visible explanation of the curious curve for the sum of the concentrations of urea and salt.

The bit of progress which we have made within the past year toward interpreting this curve is the result of remembering the importance of rate as a variable in biological processes. Thereupon we began to measure the rate of removal in urine of urea and of sodium chloride, using the simple plan of collecting individual voidings and

noting the time intervals between them. The rats were on a high salt or a high urea diet. By removing the food cups over night they were induced to eat a very large meal in the morning. The cups were then removed again and successive voidings collected over a

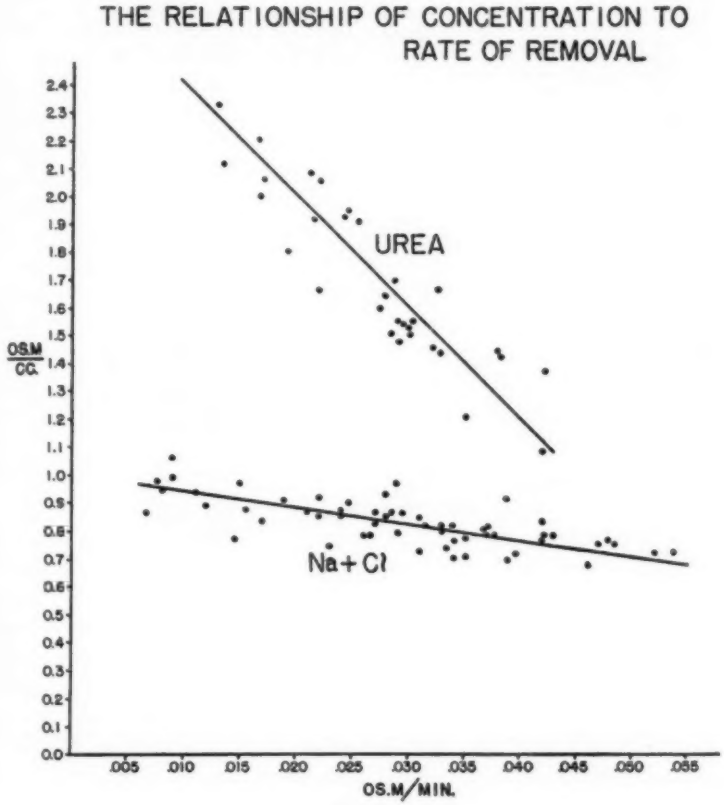


FIG. 12

period of ten or twelve hours. The data obtained in this way are recorded in figure 12 and quite clearly describe a relationship between rate of removal and concentration. Rate of removal is recorded as osmillimols per minute and has a fivefold width of change. With

increase in removal rate there is extensive decrease in the concentration of urea. The concentration of urea at the height of diuresis is less than half the value found at the slowest rate of removal. There

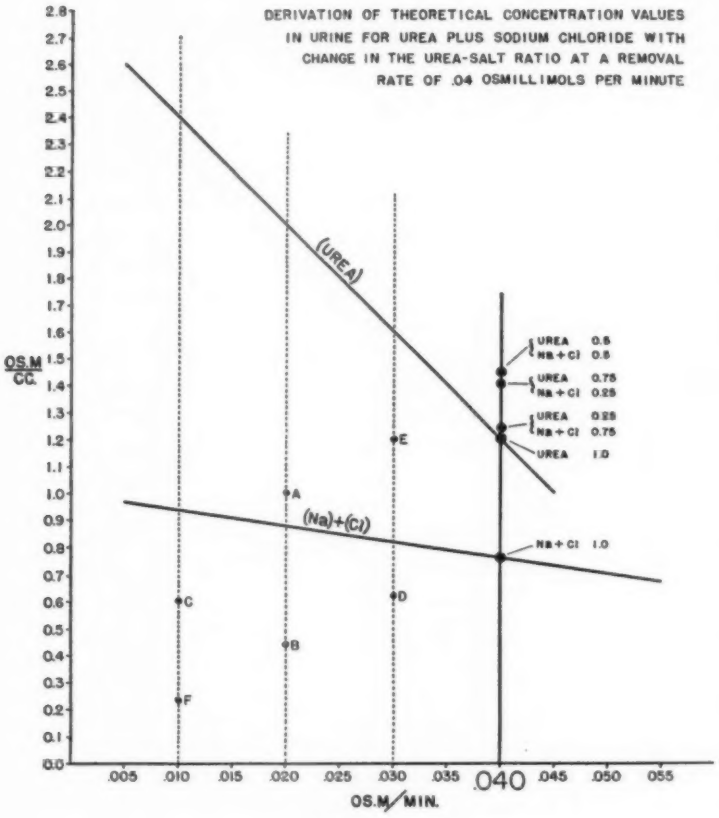


FIG. 13

is a smaller but nevertheless quite considerable range of change in the concentration of sodium plus chloride ion. In the case of urea this is not new information. Since obtaining these data we have found that evidence for this relationship between rate of removal and

concentration can be derived from data here and there in the literature. It is quite definitely visible in a study by Adolph in which the subject was of our species (9). The rats, however, by their willingness to ingest large quantities of urea or salt, and by the accuracy of their adjustment of water intake, bring the relationship into view much more clearly.

An explanation of the curve found in the urea-salt experiment can be devised on the basis of these data. I will try to indicate the path of this explanation with the help of the diagram in figure 13. The two lines which describe the relationship of rate of removal and concentration for urea and for salt respectively, when removed separately, are carried over from figure 12. A fixed value is established for one of the pair of variables. That is, 0.04 osmillimol per minute is taken as the average rate of removal of urea plus salt in the experiment which produced the concentration values, obtained from 24-hour collections of urine, which we are attempting to explain (fig. 11). We may first consider the removal of a mixture of equal parts of urea and sodium chloride at this rate. Obviously the rate of removal of urea is half the rate of removal of the mixture and is therefore 0.02 osmillimol per minute, and this is also the removal rate for sodium chloride. We note on the chart that at this rate the concentration of urea, if alone in the urine, would have a much higher value than if removed at the rate of 0.04 osmillimol per minute. One-half (A) of this higher value should therefore define water expenditure in removing urea along with an equal quantity of sodium chloride at a rate for the mixture of 0.04 osmillimol per minute. By the same steps the value (B) is derived for water expenditure in removing sodium chloride. The sum of these two values produces an expected concentration for (urea) + (Na + Cl) which is far above the values prescribed for these substances when removed separately at a rate of 0.04 osmillimol per minute. It will be understood that the concentration values (A) and (B) define the two items of water expenditure which by admixture produce the concentration value for (urea) + (Na + Cl). Obviously the individual values for (urea) and (Na + Cl) actually found in the urine when equal quantities of the two substances are removed will not be (A) and (B) respectively but must be one-half of the value for (urea) + (Na + Cl). By the same

process the values (C) + (D) and (E) + (F) produce the expected values for (urea) + (Na + Cl) when the mixtures removed at a rate of 0.04 osmillimol per minute are composed of one part of urea and three of salt, and three parts of urea and one of salt, respectively. The concentration values thus derived and recorded on the 0.04 osmillimol per minute axis are plotted in figure 14 against the urea-sodium chloride ratios. A curve is produced which has a considerable resemblance to the curve which we are attempting to explain

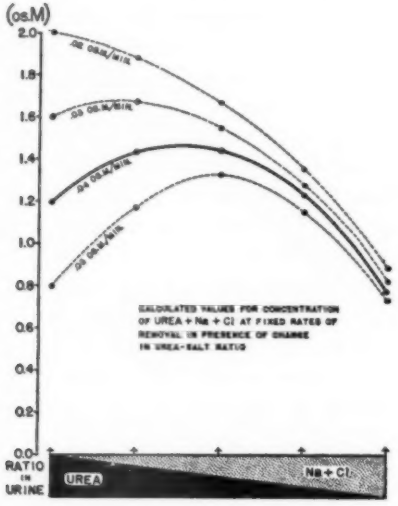


FIG. 14

(fig. 11). Taking other values for an average removal rate of urea plus sodium chloride, other curves are obtained. The curve based on a rate of 0.04 osmillimol per minute, besides resembling the curve which the experiment produced, has further support. At this rate the daily urea-salt intake would be removed in about 20 hours. The slower rates which produce the two upper curves would fall short of removing the quantity of the substances ingested.

This then is the explanation we have to offer for the curious fact that mixtures of urea and salt can be removed in urine at a much

higher concentration than can be reached by either of the substances separately. This explanation is only an hypothesis. It needs further study and testing. It contains the implication of a separateness of the mechanisms of removal of urea and salt. For this, however, there is, as you know, other evidence.

So far as we have studied the other electrolytes, they behave when removed with urea just as does sodium chloride. Since the electrolytes and urea taken together constitute more than ninety per cent of the total substances in urine, the results of these studies suggest that it may be possible to define the optimal water requirement in renal function, at least approximately, in terms of only two variables; the rate of removal of total substances and the total substances-urea ratio. The value for total substances can, of course, be readily obtained from a measurement of freezing point depression As regards the utility of such a definition; it should enable us to gain better information from the so-called concentration test of renal function. Obviously if there is, as these findings indicate, a wide range of concentration according to rate of removal of total substances and the relative quantity of urea, interpretation of a measurement of concentration should take into account the values for these two variables.

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SOME OBSERVATIONS ON INTERMEDIN*

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INTRODUCTION

In 1932 Zondek and Krohn published a series of articles in which they pointed out the use of a small fish, the *Phoxinus laevis* Ag, for the determination of an erythrophore-expanding substance. They found that the pituitary gland, chiefly the pars intermedia, contained a high concentration of such a material, and they were able to establish a biological unit, the Phoxinus Einheit (P.E.), for the substance which they named *intermedin*. Studies of the pigmentation of this fish had previously been carried on by others, Abolin particularly having made extensive researches on this subject. Since the publication of the report of Zondek and Krohn, other investigators have used this method for the biological assay of substances containing intermedin. Among these reports may be mentioned those of Astwood and Geschickter, Jores and Will, Jores and Lenssen, Giersberg, and Collin and Drouet. The majority of these authors were interested in differentiating between the melanophore- and erythrophore-expanding substances, and Jores and Will felt that the term intermedin as sponsored by Zondek and Krohn was too inclusive, and should be restricted solely to the erythrophore-stimulating fraction. The purpose of this article is not to enter into any discussion of the relative sensitivity of various chromatophore-stimulating materials, but to check some of the results in the reports of Zondek and Krohn and to bring new evidence regarding the distribution of intermedin. The term 'intermedin' as used in this report will refer only to the erythrophore-expanding substance in the various tissues examined.

* It is a pleasure to acknowledge the cooperation of Mr. Robert Fox, Superintendent of the Greenwald Packing Company.

The Assay of Intermedin. Through the cooperation of the New York Aquarium 188 elritze (Phoxinus laevis) were obtained. It was first necessary to study the response of this fish to the erythrophore-active substance. The intermedin reaction in these fish, depending as it does upon the dispersion of pigment granules in the erythrophores, varies in the area of reddening in different fish with the number and distribution of these red pigment-containing cells. It has been found that there is a great variation in these fish in the number of erythrophores. Some fish (81 of the 188 used here) had no erythrophores or so few that no gross reddening of the reactive areas was seen after the injection of potent extracts. Examination under the microscope showed that these fish had only occasional, widely separated erythrophores. Those fish which did show the reaction likewise varied so greatly in the number of erythrophores present that the red coloration ranged in extent from small localized areas at the attachment of the ventral and pectoral fins and around the mouth to a widespread redness of a large part of the ventral surface. In those fish that respond to intermedin the area of redness depends upon the number and distribution of the erythrophores and not upon the dosage of erythrophore-active substance. When this difference in the individual fish had been recognized, however, it was found that all responsive fish give a reaction to a minimum dose of intermedin in a remarkably constant fashion. The minimum dose necessary to elicit a response in any fish was so constant from one fish to another that individual differences in sensitivity were not detected during this study. The non-responsiveness of certain fish, the individual variation in area of response in others, and the negligible differences in individual sensitivity seem not to have been encountered by Zondek and Krohn, who define as a unit the minimum amount of substance necessary to elicit an area of redness of four to nine square millimeters in three out of five fish.

Those fish which were capable of responding to intermedin having been segregated, the assays were performed by injecting them hypodermically with the unknown extracts. The amount of fluid injected was kept constant at one-twentieth of a cubic centimeter, the variation of dosage being accomplished by serial dilution of the unknown solution. The unit adopted was the minimum amount of active substance which would produce a reaction in all fish receiving that dosage and the results were expressed as units per gram of fresh tissue. In other respects the methods used were the same as those described by Zondek and Krohn. Since the dilutions were usually made in multiples of two, the error in this method is in the region of plus or minus fifty per cent.

Experience with this test has shown that great caution must be exercised to prevent contamination of unknown solutions. The great stability and high activity of pituitary extracts make it very important to clean scrupulously glassware, syringes, and needles. For example, needles which have been used with highly active solutions and incompletely cleaned thereafter have been found to cause positive results when they are used for the injection of distilled water several weeks later. The need for this degree of caution was not recognized during earlier work and frequently led to confusion. The positive results on blood from a patient

with melanosarcoma as previously reported (Astwood and Geschickter) were due to contamination of the needles used for injections. The same specimen of blood as well as a second specimen from the same patient and specimens from five other cases of malignant melanomas have all given negative results since these precautions were instituted.

EXPERIMENTS

The first experiment was designed solely to find out whether the thin yellowish material noted previously by Lewis, Miller, and Matthews in the hypophyseal cleft contained any intermedin. Twenty-five beef (steer) hypophyses were cut sagittally in the midline, and the thin yellowish exudate from the clefts was put into acetone and filtered, and the residue boiled with 0.25 per cent acetic acid for one hour, according to the directions of Zondek and Krohn. This first preparation gave a very marked response.

The first experiment showed that the thin, yellow material which looked like staphylococcus aureus pus and which was scraped gently from the hypophyseal cleft with a small blunt curette contained intermedin. Apparently, Zondek and Krohn paid little attention to this substance because the only reference to cleft material is an analysis of the colloid, which they found to contain 20,000 units (Phoxinus Einheiten) per gram. They did not draw a distinction between the orange-colored colloid material which is usually found in one piece in the cleft, and this thin puslike substance described above, which will be referred to in the remainder of this article as the cleft exudate. And yet this secretion has as much intermedin as the pars intermedia itself, if not more. To test this difference quantitatively, 60 mgm. of the cleft exudate were obtained from 18 steer hypophyses, and an equal weight of pars intermedia was taken from the same glands. The two portions were treated alike—boiled gently for 35 minutes in 0.25 per cent acetic acid down to 5 cc. When assayed, it was found that the cleft exudate had 666,000 units per gram, while the pars intermedia had 500,000 units per gram.

Incidentally, the very high concentration, of 666,000 units per gram, obtained from the cleft exudate, is apparently the highest yet found, particularly when compared with Zondek and Krohn's 20,000 units per gram for the colloid.

But there are other factors which enter into these determinations.

One is that in our first experiments the cleft exudate was allowed to remain exposed to the circulating air in the room, and thus it lost moisture for the hour and a half which was required to obtain the specimens. Evaporation may well have contributed to the high readings, but of itself would not have accounted for the difference between 666,000 and 20,000.

Another factor was that the fresh gland material was placed directly in the dilute acetic acid and not first in acetone as recommended by Zondek and Krohn. In all subsequent experiments the tissue was treated in this way because it was felt that the acetone treatment was not necessary.

A third factor to contribute to the great discrepancy between the readings here obtained and those of Zondek and Krohn was their method of determining the fresh weight of the tissue fractions used. In one series of experiments they put the fresh tissue in acetone and then dissected out the six coronal zones into which they had arbitrarily divided the gland. Now, the weight of their "fresh" tissue was probably the weight of this acetone-fixed material, because there is in their publications no reference to any other method of preparation.

In order to meet the objection of dehydration as it occurred in the first experiment, the fresh tissue was placed, as before, on watch crystals as it was removed from the glands, and the watch crystals were put on pieces of cork in moist chambers. These chambers were 1000 cc. beakers, with many drops of water clinging to the inside, and inverted over several layers of towel which were dripping with water. There was, therefore, little likelihood of the fresh tissue losing any weight by evaporation.

With this precautionary measure, the cleft exudate still recorded 467,000 units per gram, and was from 10 to 20 times as strong as the determination for the colloid of Zondek and Krohn. Subsequently, another modification in the technique was made, and this latest method was used from then on to the exclusion of all others. It was employed in getting 75 per cent of the specimens, and consisted in cutting up the fresh hypophyses on the slaughterhouse floor and putting them directly piece by piece into rubber-stoppered bottles so that no moisture could escape and no postmortem diffusion could occur dur-

ing the preparation of the individual glands. It may be well to emphasize here that, in obtaining the fresh material, each gland contributed its respective portion to the whole in every preparation.

In view of the high readings for the cleft exudate, it was surprising to note that the pars intermedia itself did not contain more intermedin than the cleft exudate, or even as much. On examining comparable figures from 65 steer pituitary glands it was found that the pars intermedia averaged 257,300 units per gram whereas the cleft exudate averaged 311,550 units. Very little emphasis, however, should be laid on this difference because of the probable error in biological assays.

For the anterior lobe also a much higher concentration of intermedin was found than that reported by Zondek and Krohn. Only the anterior inferior portions of the anterior lobe were used, care being taken to avoid the lateral recesses of the cleft. In 85 glands the anterior portion of the anterior lobe averaged 27,015 units, against an average of 2857 as reported by Zondek and Krohn for 100 glands.

The pars nervosa showed a similar difference. In 85 glands the average concentration of intermedin was 30,420 units per gram, against an average of 11,904 as computed by Zondek and Krohn. This part of the gland was the most difficult to dissect in the fresh state because of its direct connection with the pars intermedia, which often almost enclosed it. For this portion of the work especially the magnifying spectacles, with a magnification of 3 diameters, and a very small-bladed scalpel were very useful.

As a further check on the data of Zondek and Krohn the walls of the third ventricle were also studied. In 26 steers the brain with the hypophysis was removed in one piece. The floor of this ventricle, extending from the infundibulum to the aqueduct of Sylvius, and having a slightly darker color than the adjacent brain tissue, was removed, and extracted twice. The assay showed the presence of 17.8 units per gram.

From these 26 specimens of brain, stalk, and hypophysis further determinations were made on the distribution of intermedin in the stalk. One portion consisted of the brain tissue at the upper end of the stalk, the tuber cinereum, and assayed 26 units per gram.

The hypophyseal stalks were divided transversely at the middle,

yielding two portions of almost equal weight. The superior fraction, near the brain, assayed 580 units per gram. The inferior fraction, however, consisting of that portion of the stalk near the gland, assayed 8070 units per gram.

It is not possible to compare the assays of the stalk and brain of cattle with any data supplied by Zondek and Krohn because these investigators did not make assays of corresponding anatomical material. The only exception is the stalk, which they found to have 500 units per gram.

Apparently no beef brains were studied and therefore the only comparative data available are of extracts obtained from the brain in a single human autopsy. In this instance the tuber cinereum yielded 15 units per gram, and the walls of the third ventricle 40 to 50 units per gram.

In view of the concentration of intermedin in the stalk at the gland, the capsule over the anterior inferior portion of the anterior lobe was removed from 32 steer hypophyses, care being taken to avoid the inclusion of any gland substance. The fresh weight of this capsule material was 1.536 grams, and it assayed 2540 units per gram.

Now, since the hormone was found in the capsule of the gland, there was a possibility that the cavernous sinus, still containing blood which came partly from the hypophysis, might also have had some intermedin. Yet the 8.76 grams of this fresh cavernous sinus material obtained from 18 steers were negative when assayed for intermedin.

Pieces of cerebral cortex, taken in one series of 14 steers from the parietal lobe near the corpus callosum, and in another series of 12 steers from the temporal aspect of the frontal lobe, failed to show any intermedin. Nor was there any intermedin in the cerebrospinal fluid which was obtained, usually free of blood, from the lateral and third ventricles of the brain while it was still in the skull. This fluid was evaporated to one tenth of its volume, and still there was no evidence of intermedin.

To what extent these observations on the concentration of intermedin in the hypophyseal stalk and brain have any bearing on the views regarding the pathway of absorption from the posterior lobe is difficult to state. It seems established that the highest concen-

trations are in the pars intermedia and in the material in the hypophyseal cleft. It would seem reasonable to believe that the progressively gradual diminution of concentration, from the pars intermedia with an average concentration of 255,000, to that part of the hypophyseal stalk near the gland with its average value of 3480 units, to that part of the stalk near the brain with a concentration of 300 units, to the brain tissue at the attachment of the stalk (tuber cinereum) with a value of 30 units, and finally to the floor of the third ventricle with 12 units, does not indicate that the stalk represents a major avenue of absorption for the intermedin. This evidence, as far as intermedin is concerned, does not support the view of Cushing, who has relied almost wholly upon histological studies and not upon biological tests, that the colloid secretion of the posterior lobe empties into the third ventricle. Recently Lennon, in studying fixed human material, as did Cushing in supporting his earlier view, found the colloid (hyaline) material in the blood vessels of the neural lobe.

On the basis of all the evidence it would seem reasonable to suppose that simple diffusion would account for the various concentrations of intermedin in the different anatomical subdivisions of the pituitary body and in the base of the brain. This view was advanced by Zondek and Krohn. To avoid some of the criticism to the effect that the diffusion was a postmortem phenomenon and did not represent the relative distribution of intermedin in the pituitary gland during life, special arrangements were made with the management on the slaughtering floor so that nine hypophyses were secured as rapidly as possible after the blood vessels of the neck of the animal had been cut. One gland was received as quickly as 6 minutes after killing; the average time for the 9 glands was $7\frac{1}{2}$ minutes. In no case did it take longer than 10 minutes before the glands were cut into the required portions and put into rubber-stoppered bottles. The assay showed the following figures: cleft exudate, 194,500 units per gram; anterior inferior portion of anterior lobe, 15,000 units per gram; posterior portion of anterior lobe, 46,700 units per gram; pars intermedia, 200,000 units per gram; posterior lobe, 9670 units per gram.

In two instances the colloid in the cleft was assayed in comparison with the cleft exudate. The pieces of colloid were caught on the point of a dissecting needle and rapidly washed in a beaker filled with dis-

tilled water. The purpose of this washing was to remove from the surface all the non-colloid material, which was known to have a high concentration of intermedin. The colloid, after being touched to filter paper which quickly absorbed the excess moisture on the surface, was put into rubber-stoppered bottles and weighed. In the first series of 32 steer hypophyses only 6 had any colloid, which weighed 0.095 grams and assayed 118,000 units per gram. The cleft exudate weighed 0.098 grams and assayed 257,000 units per gram, being thus about twice as strong as the colloid. In comparison, Zondek and Krohn found a value of only 20,000 units per gram for the 0.05 grams of colloid in 100 beef hypophyses.

Because so little colloid was found in the beef hypophyses, 46 cow hypophyses were examined. The weight of the colloid was 0.424 grams and it assayed 8500 units per gram, whereas the cleft exudate weighed 0.447 grams and assayed 237,000 units per gram. There is thus considerable difference in the concentration of intermedin in the steer as compared with the cow. Whether this difference is of any significance, and whether the colloid of the thyroid gland has similarly a lower concentration of its active principle than the fluid immediately surrounding it, can only be conjectured.

Zondek and Krohn frequently mentioned the stability of intermedin despite the thorough boiling of the tissues. To test this point, two equal portions of the anterior inferior part of the anterior lobe of 17 steer hypophyses, each half weighing 0.940 grams, were boiled respectively 33 and 266 minutes in 0.25 per cent acetic acid. The assay showed that the fraction that had been boiled the shorter time had 46,800 units per gram, whereas the other portion had 22,600 units. It is possible, then, that repeated boiling, with its resulting concentration of the acetic acid, may partly destroy the intermedin. However, too much stress should not be put on this difference because of the possibility of large error in these biological assays.

Finally, a word may be said regarding the histology of the steer hypophysis. As regards the cleft exudate, this was stained in the fresh state with numerous reagents, including Wright's blood stain, Mann's stain, toluidin blue, methylene blue, and neutral red. In addition, some of this fresh material was fixed in Zenker's fluid, imbedded, and then sectioned; other portions were put into a dilute

gelatine solution and then fixed in Zenker's fluid. Furthermore, serial sections were made of a steer hypophysis and pilot sections were stained in hematoxylin and eosin. All these methods showed that the cleft exudate consisted almost entirely of desquamated epithelial cells and that these cells could be shown in some sections to extend from the pars intermedia into the cleft. There is no doubt that some of the small cuboidal cells lining the anterior aspect of the cleft also were present, but the predominating cell was almost solely from the pars intermedia. This histological evidence supports the finding of the high concentration of intermedin in the cleft exudate.

In order to obtain a better idea of the cells in the steer hypophysis, sections of tissue obtained from the various parts of such a gland, cut from 3 to 5 micra thick, were treated with the following stains: hematoxylin and eosin, iron hematoxylin and eosin, Mallory's connective-tissue stain, Mann's, Severinghaus', and Spark's. Of all these methods, Spark's stain proved the best for the purpose at hand: namely, to see whether basophilic cells played any part in the formation of intermedin. With this stain the basophilic cells showed a bright blue color and could be readily identified. No basophilic cells were found in the pars intermedia of the steer hypophysis. The pars anterior of the same gland, however, had cells which may have been basophiles but for certain differences, the greatest of which was that the cytoplasm stained a very faint uniform blue color. The cytoplasm was not granular, but appeared in small sheets, with frequent round clear open places resembling faint vacuoles. The nucleus was smaller than the nucleus of the eosinophile and its chromatin was also less. The whole cell was invariably much smaller than the eosinophile and was infrequently seen. It is possible that these cells were basophiles originally but show this change because of castration. As a check, sections prepared in an identical manner were taken from corresponding portions of the cow hypophysis, and these sections showed masses of deep-blue-staining basophiles in the anterior lobe, but none in the pars intermedia. It seems that the finer histology of the pars intermedia of the hypophysis in cattle is even now not known very well. A helpful description was furnished by de Beer in his book published in 1926.

Since the highest concentration of intermedin was found to be in

the pars intermedia and in the cleft exudate, it is reasonable to believe with Zondek and Krohn that this part of the gland furnishes the intermedin. In view of the fact that no basophiles were found in the pars intermedia or in the cleft exudate, it seems safe to conclude that the basophiles do not form the intermedin.

Table 1 summarizes briefly the majority of the assays. Each

TABLE 1

Intermedin content of various portions of the hypophyses of cattle

	UNITS PER GRAM OF TISSUE (FRESH WEIGHT)									TOTAL NUMBER
	Steers							Cows		
	1	2	3	4	5	6	7	8	9	
	Number of hypophyses									
	20	4	18	9	32	14	12	24	23	156
										Average
Pars intermedia	151000		421000	200000				313000	181000	255000
Cleft exudate	468000		227000	194000	257000			144000	330000	270000
Cleft colloid	357000				118000			11800	5200	123000
Pars neuralis	46000		41000	9670	245000			46600	31200	33200
Anterior lobe, posterior part			15000	46000						30800
Anterior lobe, anterior part		21800	24000	15000	46800			5400	4250	19600
Anterior lobe, capsule					2540					2540
Stalk-inferior (gland) part	910	1470					8070			3480
Stalk-superior (brain) part		68				133	1000			300
Tuber cinereum		10				30	22			30
Third ventricle		2				19	16			12
Cerebral cortex						0	0			0
Cerebrospinal fluid		0				0	0			0
Cavernous sinus		0								0

column represents the assay of extracts as obtained from that number of hypophyses mentioned at the top. The last column, giving the averages, shows not only the relative concentrations of intermedin in the gland itself, but it also emphasizes the progressive diminution of this concentration with the increase of distance from the gland.

Zondek and Krohn proposed a chemical method for the purification

of intermedin, and they were able to obtain a preparation which contained 1 unit in 1 gamma of dry powder (1,000,000 units per gram). However, using the methods as described in this paper, it was found that fresh, untreated pars intermedia contained, on an average, 255,000 units per gram of wet tissue, or 1,785,000 units per gram when expressed in the form of dry powder. Simple extraction with 0.25 per cent acetic acid without further chemical treatment resulted in a concentration of the active substance that in terms of dry weight averaged at least 5 units per gamma.

The reason for this higher concentration may be threefold. In the first place, it is quite possible that Zondek and Krohn lost some intermedin when they first treated the glands with acetone. In the second place, all of the glands used here were freshly prepared, and the danger of losing intermedin through deterioration of the fresh material was avoided. And finally, since all the test fish were known to react positively to a sufficient dose, a higher average of sensitivity was obtained.

SUMMARY

The work of Zondek and Krohn on the concentration of intermedin in the hypophysis of cattle was repeated with some modifications. Values were obtained which were from 5 to 20 times as great as those reported by these investigators. The yellow puslike material in the cleft showed the highest average values, being closely followed by the pars intermedia. This cleft exudate consisted of desquamated cells from the walls of the cleft, chiefly from the pars intermedia. The colloid material in the cleft had a lower concentration. The hypophyseal stalk and the region about the third ventricle of the brain contained progressively less intermedin the further the samples of tissue were taken from the pituitary gland. The capsule of the gland contained intermedin, but the cavernous sinus did not. It is probable that diffusion is responsible for these various concentrations. Because of the absence of typical basophilic cells in the pars intermedia of the hypophysis of cattle, as judged by the use of Spark's stain, it is believed that intermedin is not formed by these cells.

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A SIMPLE METHOD FOR THE ANALYSIS OF HELIUM[1]

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Barach (1) has recently introduced helium as a therapeutic gas in the treatment of respiratory obstructions. Investigation of this problem has been hampered by the fact that no inexpensive apparatus has been available for the analysis of gas mixtures for helium. The purpose of this paper is to report a simple method which has given satisfactory results in our hands.

When helium is used as a therapeutic agent one is dealing essentially with a three-gas system—oxygen, helium and nitrogen. The concentration of carbon dioxide can be maintained at negligible levels. Under theoretically ideal conditions nitrogen would be excluded from the system entirely but this is seldom practical. Furthermore, leaks in the oxygen-helium tent system manifest themselves as increases in the concentration of nitrogen. This gas, therefore, must be reckoned with in any method of analysis.

In the usual systems of gas analysis, the various other constituents are absorbed by chemical agents leaving nitrogen, a practically inert gas, to be measured as residue. However, helium is even more inert than nitrogen. For this reason any method of analyzing gas mixtures containing both nitrogen and helium must depend on the physical rather than the chemical properties of these gases.

From Graham's Law it can be shown that the times of effusion, at constant temperature, of equal volumes of two different gases through the same small aperture and under the same difference of pressure, are proportional to the square roots of the densities of the two gases. Thus, if the time of effusion of an unknown gas is compared, under standard conditions, with the time of effusion of a gas of known den-

[1] The helium used in this study was made available by the coöperation of the United States Public Health Service.

sity, the density of the unknown gas can be calculated. If we are dealing with an unknown mixture of two pure known gases like helium and nitrogen, the proportions of each gas in the mixture can be determined from the density of the mixture as measured by the effusion method. Furthermore, with a mixture of three pure gases, as helium, nitrogen and oxygen, the relative proportions of any two of the gases can be determined if the concentration of the third gas and the density of the mixture be known. These principles have been utilized in the method of analysis here described. We are dealing with a mixture of oxygen, nitrogen and helium. The mixture is analyzed for oxygen by any of the simple known methods and the rate of effusion of the mixture is determined relative to the effusion time for atmospheric air as standard. By referring these values to curves on a calibration graph for the particular apparatus used, the concentrations of helium and of nitrogen can also be determined.

Description of the Apparatus. In fig. 1 is shown a drawing of the apparatus. A glass tube 16 inches in length has at its center a bulb of approximately 50 cc. capacity. To the lower end of the tube a leveling bulb of 125 cc. capacity is attached by means of rubber tubing and filled with ethyl alcohol to which a little safranin has been added to give color. At the upper end of the tube is fastened a three-way stopcock (B) and to one arm of this a second three-way stopcock (A) is fixed. To the other arm is cemented the effusion disc, held in a small metal screw clamp as shown in the detail drawing. The effusion disc is $\frac{9}{16}$ inch in diameter and cut from aluminum 0.005 inch thick. At the center is drilled a hole 0.005 inch in diameter. About one inch above the bulb a mark is placed on the tube. The whole apparatus is mounted on a board to which two open rings have been rigidly fixed in order to hold the leveling bulb at two arbitrary positions (position A and position B).

Method of Analysis. Room air is drawn into the tube and bulb through stopcocks A and B by lowering the leveling bulb to position A. Stopcock B is then closed and the leveling bulb raised to position B. Stopcock B is turned so that the air, now under pressure in the tube, escapes through the orifice in the effusion disc. A stopwatch is started the moment stopcock B is turned and the time measured for the fluid level to rise to the mark on the tube. The same procedure

is now repeated using the unknown mixture of gases, but in order to insure against dilution of gas, the apparatus, including the effusion disc, is first flushed several times with the gas mixture by means of stopcock A. The ratio of the time of effusion of the unknown gas

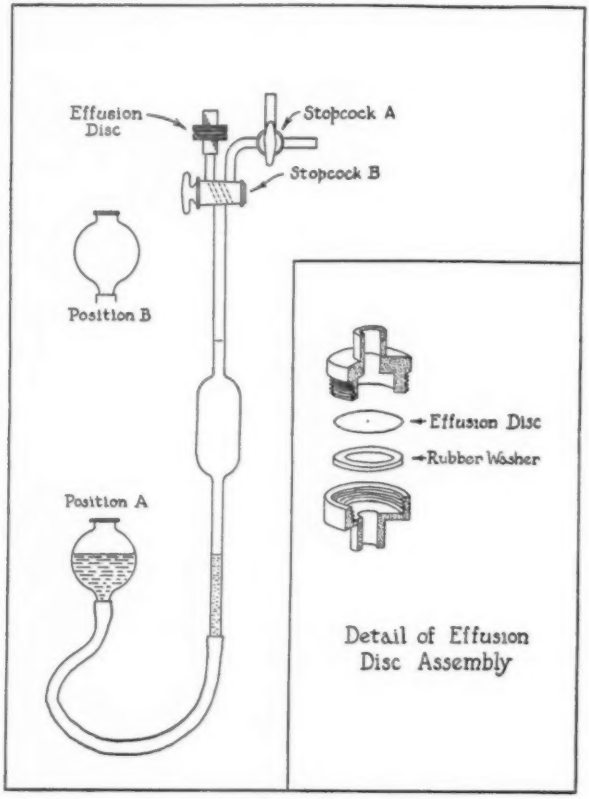

FIG. 1. DRAWING OF THE HELIUM ANALYSIS APPARATUS

mixture to the time of effusion of atmospheric air we have termed the effusion ratio. A sample of the unknown gas mixture is now analyzed for oxygen by any standard method. The values for the concentration of oxygen and the effusion ratio are referred to the calibration

curve for the apparatus and from it may be read the concentrations of helium. The residue is nitrogen.

The Calibration Curve. The apparatus is calibrated by determining first the effusion time for oxygen. From this value are calculated the effusion times for helium, nitrogen and various mixtures of the three gases, according to the formula:

$$E_1 : E_2 = \sqrt{D_1} : \sqrt{D_2}$$

where E = effusion time and D = density of gas.

TABLE 1

Calculated and observed effusion times and effusion ratios of various mixtures of helium, oxygen and nitrogen

COMPOSITION			ATOMIC WEIGHT	EFFUSION TIME			EFFUSION RATIO	
He	O_2	N_2		Calculated	Observed	Per cent difference	Calculated	Observed
per cent	*per cent*	*per cent*		*seconds*	*seconds*	*seconds*		
	100		16.0		87.0			1.05
	40	60	14.8	83.7	84.4	0.8	1.01	1.02
	20	80	14.4	82.7	83.0	0.4	1.00	1.00
		100	14.0	81.5	81.8	0.4	0.99	0.98
20	80		13.6	80.3	80.7	0.5	0.97	0.97
20	40	40	12.8	77.9	78.2	0.4	0.94	0.94
20	20	60	12.4	76.6	77.4	1.0	0.93	0.93
20		80	12.0	75.3	76.2	1.2	0.91	0.92
50	50		10.0	68.8	70.1	1.9	0.83	0.84
50	20	30	9.4	66.7	67.6	1.4	0.81	0.82
50		50	9.0	65.2	65.8	0.6	0.79	0.79
80	20		6.4	55.0	55.8	1.5	0.66	0.67
80		20	6.0	53.4	53.8	0.8	0.65	0.65
100			4.0	43.5	44.1	1.4	0.53	0.53

Since the densities are proportional to the atomic weights, the formula may be rewritten

$$E_1 : E_2 = \sqrt{A_1} : \sqrt{A_2}$$

where A = atomic weight of the gas.

For mixtures of gases the equivalents of the atomic weight are calculated from the proportions of the various gases in the mixtures (see table 1).

From the effusion times as calculated by the above method, the effusion ratios of the various gases and mixtures are determined, the effusion time for atmospheric air being considered unity. These values, when plotted as abscissae on a graph, with the concentration of helium expressed in per cent, as ordinates, complete the calibration

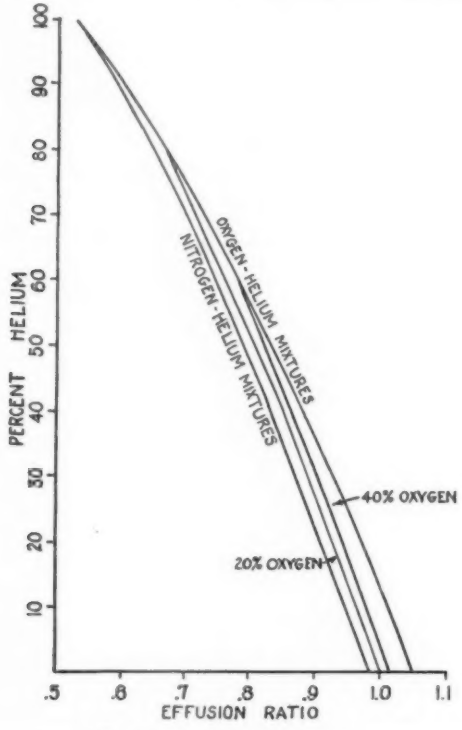

FIG. 2. CALIBRATION CURVE

curve. As can be seen from fig. 2 several lines are drawn for various oxygen concentrations. One curve is for helium-nitrogen mixtures and represents the graph for zero oxygen concentration. At the other extreme is a curve for helium-oxygen mixtures and in intermediate positions lie graphs representing various intermediate oxygen concentrations.

When a mixture of oxygen, helium and nitrogen of unknown concentrations is analyzed, the content of oxygen in per cent and the effusion ratio are determined as described above. The value for the effusion ratio is marked on the curve corresponding to the correct oxygen concentration. The ordinate of this point gives the per cent concentration of helium in the gas mixture. The nitrogen content is calculated by subtracting the sum of the per cent concentrations of oxygen and of helium from 100.

In calibration curves used by us we have determined the graphs only for oxygen concentrations of 20 and 40 per cent. Oxygen is never used therapeutically in less than 20 per cent concentration and when used with helium would never exceed 40 per cent. For intermediate oxygen concentrations, the values are interpolated between the appropriate curves.

Accuracy of Method. For clinical use there is no need for accuracy greater than the nearest 5 per cent value. Under ordinary working conditions the error of the method falls well within this limit. It can be seen from Table 1 that the discrepancy between the observed effusion time and the calculated value was always less than 2 per cent. Variations in atmospheric pressure have no effect on the results because both the gas mixture under analysis and the atmospheric air are equally affected. Variations in temperature of the gas mixtures drawn from the helium-oxygen chamber cause no significant errors unless the temperatures differ greatly from that of room air. In this case the gas is allowed to stand in the apparatus for a few minutes until the temperatures have equilibrated. Differences in humidity of the chamber gas from 20 to 100 per cent saturation cause no appreciable variations in the readings.

SUMMARY

An inexpensive apparatus and a simple method have been described for the analysis of helium in helium-oxygen-nitrogen mixtures. The method is useful in determining the concentrations of helium in tents or chambers in which this gas is used therapeutically.

REFERENCE

(1) Barach, A. L.: The Therapeutic Use of Helium, *J. A. M. A.*, **107**, 1273, 1936. This article includes a complete bibliography on the subject.

QUININE AS AN ADJUVANT TO PROSTIGMIN IN THE DIAGNOSIS OF MYASTHENIA GRAVIS. A PRELIMINARY REPORT

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It has been shown recently (1, 2) that prostigmin is of value in establishing the diagnosis of myasthenia gravis. There are some cases of this disease, however, in which the symptoms are so mild that the diagnostic test with this drug is not conclusive. Kennedy and Wolfe (3) were the first to point out that quinine has an antagonistic action to prostigmin in cases of myasthenia gravis. In the course of some observations in relation to this action of quinine, the authors have used the drug in establishing the diagnosis of myasthenia gravis in a case with few objective signs.

H. R. (U. 107740). This patient was a 27 year old, white, single miner who was admitted to the Johns Hopkins Hospital complaining of double vision. The family history was non-contributory. His past health had been excellent. Before the present illness he had been strong and active. He had worked as a farmer and miner. For a number of years he had played semi-professional baseball. Eighteen months before admission he noted that, after working with his head bent, he had difficulty in extending his neck. Thirteen months before admission his arms began to tire after use, and this symptom increased until he could no longer throw a baseball. At the same time he found that he could walk only short distances before his legs became tired. These symptoms progressed, so that six months after their onset, he was forced to give up all work. During the past nine months his arms would become fatigued even by shaving and combing his hair. Speech occasionally sounded thick after prolonged talking. The patient was troubled by double vision, and the right eyelid drooped at times. The symptoms were all increased by activity and disappeared almost entirely after rest.

Physical examination showed a healthy young male who appeared quite strong. His actual strength, however, was not very great, and his arm and leg muscles tired after moderate use. Only after repeated exercise of the extra-ocular muscles did diplopia develop with slight ptosis of the right lid. No other signs or symptoms of myasthenia gravis could be elicited. The patient was also suffering from a subacute gonorrheal urethritis.

He was given prostigmin, 1.5 mgm., subcutaneously. Diplopia and slight ptosis of the right eyelid were present before the injection. About five minutes after the prostigmin had been given the ptosis lessened, the diplopia decreased, and

the patient felt generally stronger. He was able to exercise more before fatigue set in. However, the signs were never sufficiently pronounced to permit definite conclusions as to improvement. For a week prostigmin was administered orally, 30 mgm. three times a day. During this period the patient noted a decrease in the symptoms which had brought him to the hospital, and he continued to feel relatively well during a week in which he received no medication. He was then given quinine sulphate, 0.6 gm. four times a day by mouth. After a total of 2.4 gms. of quinine there developed definite ptosis of the right eyelid, internal strabismus of the right eye, and general weakness so marked that the patient had to be fed. The quinine drug was continued in this dosage for three days. At the end of that time the ptosis and internal strabismus were constant, subjective weakness was extreme, and objectively the arm, leg and jaw muscles had little power. Prostigmin (3 mgm.) was then injected subcutaneously. Within seven minutes and lasting for about forty-five minutes, there was marked improvement in the signs and symptoms. In contrast with the equivocal effects produced by prostigmin before quinine, the results elicited by a single dose of prostigmin, after the administration of quinine, were of conclusive diagnostic significance.

DISCUSSION

In the case reported the increase in symptoms after the administration of quinine was promptly relieved by the injection of prostigmin, which had caused little noticeable change before the weakness was made prominent by the use of the antagonistic drug. That caution is necessary in giving quinine to patients with myasthenia gravis is indicated by the results in a second case in which alarming symptoms appeared after the administration of 1.2 gm. of the drug, although 90 mg. of prostigmin were given orally during the same period of time. This man had moderately severe symptoms before the experiment was carried out. Prostigmin given subcutaneously alleviated this distress, but the duration of its action was considerably reduced.

CONCLUSIONS

In an occasional case of myasthenia gravis the objective signs of the disease may be so slight that the diagnostic test with prostigmin is inconclusive.

In an instance of this type the administration of quinine increased the symptoms to such a degree that the improvement following the injection of prostigmin was easily recognized.

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(3) Kennedy, F., and Wolf, A.: Experiments with Quinine and Prostigmin in Treatment of Myotonia and Myasthenia. *Arch. Neurol. and Psych.*, **37**, 68 (Jan.) 1937.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

The Colon as a Health Regulator—From a Surgeon's Point of View. By SIR HENRY M. W. GRAY. 100 pp. Illus. $2.50. (*Toronto: The Macmillan Company of Canada, 1936.*)

The author attempts to establish the thesis that common anatomical variations in the colon, variations which are of developmental origin, produce local and general symptoms of many kinds. He says that the surgical correction of these variations will, in selected cases, give relief to a large number of so-called hypochondriacs, mal-nourished persons, persons afflicted with "chronic infective diseases," and epilepsy. He finds too, that the operation has helped those who had "discolouration of the skin, chronic acne-like eruptions, unhealthy complexion, 'inability to put on flesh' or 'loss of flesh', anaemia, early senile changes, pains or other 'rheumatic' manifestations, irritability, nervousness, brain fag, attacks of sudden faintness, . . . want of energy or general vitality, . . . liability to various infections, . . . decay of teeth, halitosis, and, . . . functional and ultimately organic disturbance of any of the tissues or organs of the body."

The style may be described as "chip-on-the-shoulder" and the author expects "less privileged members of the profession . . . to cast the book aside as being another fantastic result of a gospel preached by Sir William Arbuthnot Lane." He is, however, sincere in his belief that "developmental abnormalities are the primary cause of most of the morbid conditions, barring pelvic complaints, for which the surgeon opens the abdomen." He cites a few case histories; he describes the anatomical variations in the form and attachments of the colon; he names the effects which he believes these produce, and he describes his operation for a "house cleaning" of the developmental anomalies.

One lays the book on a high shelf and remarks that every person is entitled to his own views about the colon as well as about the political situation.

J. T. H.

Reading, Writing and Speech Problems in Children. By SAMUEL TORREY ORTON. 215 pp. Illus. $2.00. (*W. W. Norton & Company, New York, 1937.*)

This book contains the fourth of the Thomas W. Salmon Memorial Lectures and presents a condensed summary of ten years' research in the disorders of development of language faculty. In the Introduction Dr. Orton describes briefly the usual course of the development of speech and writing, and in the remainder of the book, which is divided into three chapters, discusses possible developmental defects, a theory of etiology and methods of treatment.

In Chapter I, "Language Losses in the Adult as the Key to the Developmental Defects of Children," Dr. Orton briefly considers a few of the acquired disorders of speech in adults and points out the fact that there is no speech defect unless the lesion involves the dominant hemisphere. In this is the key to developmental defects in the acquisition of language by children, he believes. He finds that trouble arises when there is a mixture of right- and left-sidedness—"Intergrading."

In the second Chapter, "Certain Disorders in the Development of Language in Children," the author discusses in detail the presenting symptoms of the specific reading, writing and speech disabilities, word deafness, abnormal clumsiness and stuttering. The effect of these disabilities upon the child's conduct and emotional attitude is also considered.

In Chapter III, "Interpretation and Treatment of Certain Disorders of Language in Children," Dr. Orton gives his theory as to the cause of these disabilities and this includes the concept of engrams—"a physiological record" of a stimulus—being present in opposite hemispheres in antitropic form and by this explains reversals and mirror reading and mirror writing. The major portion of this chapter takes up the treatment of each of the main disorders discussed in the second chapter.

This book presents Dr. Orton's theories concerning speech disorders and their treatment. The glossary of terms aids those unfamiliar with his terminology. Many will be inclined to question the neurological interpretation offered, but the book gives a clear, brief, factual presentation of the various disorders in speech development and offers definite help and advice with regard to their treatment.

M. R.

Diseases of the Respiratory Tract. Clinical Lectures of the Eighth Annual Graduate Fortnight of the New York Academy of Medicine. By 21 contributors. 418 pp. Illus. $5.50. (*W. B. Saunders Co., Philadelphia, 1936.*)

Annually for eight years, the New York Academy of Medicine has conducted what it terms "A Graduate Fortnight," during which some one clinical subject of importance is presented in such fashion as to "offer to the profession a grasp of the advances in medicine so that the busy practitoner may be informed from authoritative source as to the last word on a given topic."

"Diseases Of The Respiratory Tract" is made up of a group of twenty articles, each of which deals with some malady of the air-ways. The author of each article is an authority in his special field. The topics dealt with are of living interest and the facts presented are informative. Though much of the material is not new to workers in specialized fields and though some of the opinions expressed are still controversial, the publication of such as part of a symposium dealing with diseases encountered by the practicing physician fills an educational purpose. The volume is an excellent treatise giving current views on subjects as varied as the common cold, sinusitis, carcinoma of the lung, bronchiectasis, the immunity and the surgery of tuberculosis, emphysema, pneumonoconiosis, etc.

The publication may be commended highly.

C. R. A.

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PROBLEMS IN ACTIVE AND PASSIVE IMMUNITY[1]

THORVALD MADSEN, CLAUS JENSEN AND JOHS. IPSEN

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Even though nearly fifty years have passed since the first demonstration of antitoxin, we are as yet far from knowing for sure *where* antitoxin is produced. On the other hand, we have at our disposal a considerable material dealing with the quantitative aspects of antitoxin production. In the later years, however, the interest in this question has been waning, but the antitoxin curve still presents so many problems that it would certainly be worth while to examine them fairly thoroughly. As you know, Brieger and Ehrlich (1) were the two first in 1893 to demonstrate variations in the antitoxin content of the milk in goats immunized against tetanus, and in 1896 Salomonsen and Madsen (30) obtained a similar curve on subcutaneous immunization of horses with diphtheria toxin. They established three phases in the antitoxin curve: (1) a fall—the so-called negative phase—which is followed by (2) a rise. When this has reached its maximum, there comes (3) a fall—the third phase. Subsequently this undulating antitoxin curve has been demonstrated for many other antigens, differing according to the nature of the antigen, the manner of its application and the animal species—and a great deal of work has been done in this field by the State Serum Institute at Copenhagen. In spite of all differences, however, we still find, on the whole, the same fundamental features in the course of the curve.

An analysis of the individual phases on the curve naturally falls into three parts. As to the *third* phase, it shows a close agreement with findings in passive immunity, *i.e.*, what we find on introduction of antitoxin from an actively immunized animal into the blood stream of a normal organism: the antitoxin concentration of the blood reaches at once its maximum, and then falls off along the line of a curve which is found to resemble the third phase of the antitoxin curve in active

[1] Herter Lecture delivered by Th. Madsen, February 24, 1937, at the Johns Hopkins University School of Medicine.

immunity. It was demonstrated already long ago[2] that the fall of the curve in this phase both in active immunity and in passive immunity may be expresssed by a simple formula:

$$\frac{dx}{dt} \cdot \frac{1}{x^{n+1}} = K$$

where x is the amount of antitoxin, t the time, and n and K constants characteristic of each case. You see that this formula embodies the

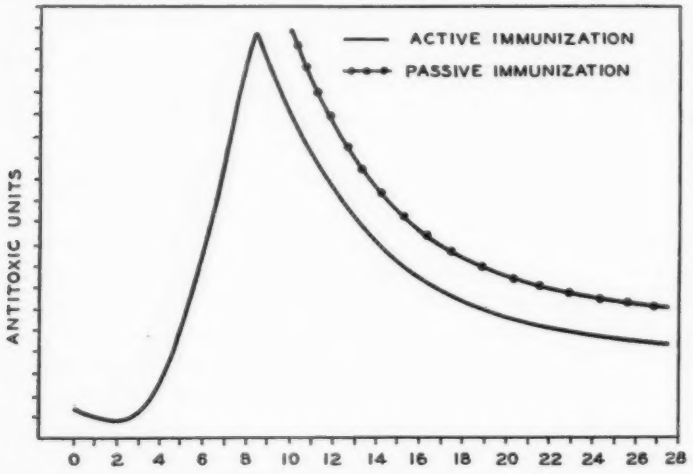


FIG. 1. COMPARISON BETWEEN THE 3 PHASES OF AN ACTIVE IMMUNITY CURVE AND A PASSIVE IMMUNITY CURVE

more common chemical reaction formulas: the monomolecular when $n = 0$, the bimolecular when $n = 1$.

The latter is the case in the third phase in *active* immunization against diphtheria, whereas the *passive* curve for diphtheria antitoxin is not quite as simple, which may be illustrated by the following example[3]:

[2] Th. Madsen: The decrease of antibodies in the organism indicated by a formula. Festskrift v. Indvielsen af Statens Seruminstitut, 1902.

[3] Madsen, *l. c.*

FIG. 2. PASSIVE IMMUNISATION IN AN ASS

t	x OBS.	x CALC. ($a = 0.2$)
0	15	15
4	6.0	5.2
8	2.5	2.2
12	1.0	1.0
16	0.5	0.53

If we try to get some idea of what happens to the antitoxin we find nothing to suggest that *excretion* is essential. Only very small amounts of antitoxin are found in excretions such as urine, saliva, sweat, tears, etc. On the other hand, the formula rather suggests a process of deterioration, though naturally we have to be very cautious in drawing conclusions from a mere numerical agreement.

In this connection, I think, it will be appropriate to call attention to some previous experiments[4]:

FIG. 3. DETERIORATION OF DIPHTHERIA ANTITOXIN BY HEATING

TEMPERATURE 74.1°			TEMPERATURE 72.05°		
min. (t)	AU (obs.)	AU (calc.)	min. (t)	AU (obs.)	AU (calc.)
0	50	50	0	70	70
4	25	25	7	35	37.7
7	20	19.2	15	25	25
15	12	11.4	20	20	20.4
20	10	9.1	30	15	15.3
40	5	5	50	10	10
60	2	3.4	80	7	6.7
			110	5	5
$K = 0.0045$			$K = 0.0017$		

TEMPERATURE 70.0°			TEMPERATURE 67.95°			TEMPERATURE 65.75°		
min. (t)	AU (obs.)	AU (calc.)	min. (t)	AU (obs.)	AU (calc.)	min. (t)	AU (obs.)	AU (calc.)
0	75	75	0	[80]	68	0	80	80
10	45	51.3	10	60	60	30	65	64.9
30	25	31	30	45	48	60	55	54.9
60	20	19.4	60	35	37	120	40	43.5
100	15	13	90	30	30	180	35	35
150	10	9.2	120	25	25	360	25	22.5
180	7	7.8	180	20	19			
			240	15	15.4			
$K = 0.00064$			$K = 0.00022$			$K = 0.000089$		

[4] Madsen and Walbum: Difteriantitoxinets Svaekkelse. Seruminstitutets Festbind, 1917.

We found that the deterioration of diphtheria antitoxin by heating might be expressed by the bimolecular formula, that is, the same formula that applies to the 3rd phase in active immunity.

This process is largely dependent upon the temperature, and may be expressed by the well known vant Hoff-Arrhenius formula:

$$\frac{K_1}{K_2} = e^{\frac{M}{2}\left(\frac{T_1 - T_2}{T_1 T_2}\right)}$$

How good the agreement is, will be evident from the values recorded in Fig. 4.

FIG. 4. SYNOPSIS OF FIG. 3

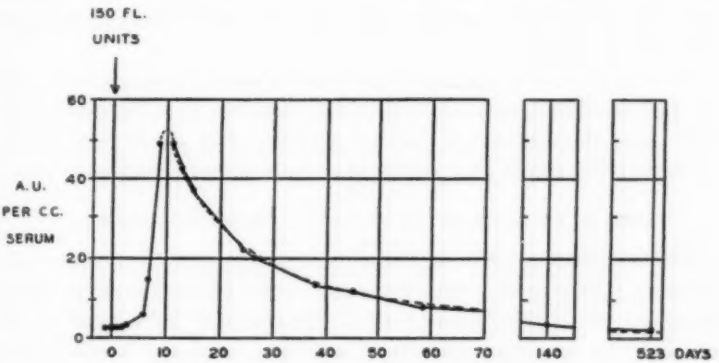
TEMPERATURE	K (OBS.)	K (CALC.)
74.10°	0.0045	0.0045
72.05	0.0017	0.00176
70.00	0.00064	0.000648
67.95	0.00022	0.000267
67.75	0.000089	0.000088

Thus the temperature coefficient is very high—110,800—and this means that there would be no deterioration of the antitoxin at all at body temperature. On the other hand, at lower temperatures (5–25°) we found the temperature coefficient to be only one-tenth of the above (11,100). I regret to say that we have no data on deterioration of diphtheria antitoxin at body temperature. It looks rather strange that the temperature coefficient should thus vary in different regions of temperature, and further experiments dealing with this question would be very desirable.

Particular attention has been paid to the so-called *negative phase*, which is most conspicuous when antigen is injected in the 3rd phase of the antitoxin curve or still later, when the antitoxin has reached a sort of balance, *i.e.*, when the fall has become very slow. This negative phase has attracted considerable interest; it has been the subject of much discussion and different interpretation—among other reasons, because it was feared that vaccination of human beings (for example, at the outbreak of a threatening epidemic) might give a negative phase and in this way lower the resistance of the vaccinated subjects, at any rate for some days. In studies dealing with this problem especially, however, it has been shown that there is no foundation for such a fear.

Many of these problems have been left unsolved, for one reason, because their investigation on any fairly large scale with the old technique for estimation of diphtheria antitoxin would require a quite disproportionately large number of animals. Since we now have at our disposal a greatly improved technique for measuring antitoxin, as given by Claus Jensen, we have taken up the old problem anew.

Claus Jensen[5] has elaborated the old intracutaneous technique, which was published originally by Römer, in such a way as to make



THE EFFECT OF A SINGLE SUBCUTANEOUS INJECTION OF CONCENTRATED AND PURIFIED DIPHTHERIA FORMOL TOXOID IN A 12 YEAR OLD CHILD HAVING 2 ANTITOXIC UNITS IN THE BLOOD BEFORE THE INJECTION.

•—•—• OBSERVED VALUES

– – – – – CALCULATED VALUES

FIG. 5

it possible with great accuracy to measure an amount of diphtheria antitoxin as low as 0.00005 A. U. per c.c., and by employment merely of a relatively very small number of animals (rabbits).

It has always been a problem how it could happen that the injection of a toxin into an actively highly immunized animal might bring about a production of antitoxin. A simple calculation will show that the injected amount of toxin will be neutralized by a fraction of the

[5] Claus Jensen: *Die intrakutane Kaninchenmethode.* Copenhagen, 1933.

amount of antitoxin present in the organism. With a *subcutaneous* injection one might perhaps imagine that different conditions of absorption would assert themselves, but this does not apply to *intravenous* injection. Some authors have even gone so far as to assume that the conditions of fixation between toxin and antitoxin would be different in the blood stream.

I shall show you first the curve for a child[6] who was immunized actively with formol-toxoid. You will notice the close agreement between the value obtained and the value calculated in accordance with the bimolecular formula—and this was even as long as $1\frac{1}{2}$ years after the immunization.

This fact, that we are able by means of these formulas to calculate the course of the decrease of antitoxin in passive and active immunization offers the advantage that we are able with great certainty to estimate the result of an injection of antigen upon the antitoxin curve.

EFFECT OF ANTIGEN ON ACTIVELY IMMUNIZED ANIMALS

The animals employed in these experiments were all given a preliminary stimulus to antitoxin production by subcutaneous injection of about 30 Fl. U. formol-toxoid. One month later their blood contained a moderate amount of antitoxin, and the animals were able to withstand several, otherwise lethal, doses of toxin injected intravenously.[7]

It will suffice here to give the curves from one experiment (Fig. 6), as the other experimental results in all essentials correspond to these findings.

Rabbit No. 715 is immunized subcutaneously with 30 Fl. U. formol-toxoid. One month later it is able to survive 10 lethal doses of diphtheria toxin given intravenously. This latter injection produces an additional increase in the antitoxin concentration, and the experiment proper begins 22 days after this injection—after three antitoxin titrations have shown that the antitoxin curve is in the last part of

[6] Claus Jensen: *Acta Pathologica et Microbiologica Scandinavica*, Vol. X.

[7] In numerous immunizing experiments on rabbits, Th. Madsen, Claus Jensen and S. Schmidt have proved that rabbits with over 0.02 A. U. per c.c. of serum survive 10 d.l.c., whereas rabbits with a lower antitoxin concentration are overcome by the same dose.

the third phase. The further course of the curve can then be established as indicated by the stippled line.

Now the intravenous injection of 100 lethal doses of toxin produces the typical three phases: a distinctly negative phase, which gradually

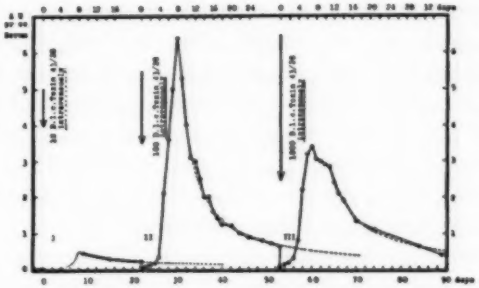


FIG. 6

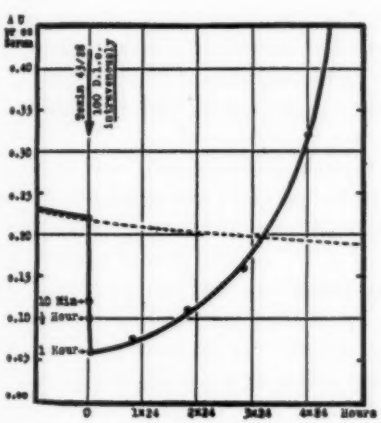


FIG. 6a

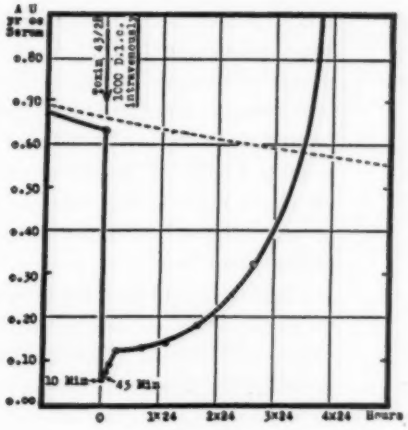


FIG. 6b

turns into a second phase, an almost linear rise to the maximum on the 8th day, and then the third phase with regular fall in close agreement with the calculated curve—this is also indicated by a stippled line.

Some time later a similar experiment is performed on the same rabbit with injection of 5 c.c. of toxin—*i.e.*, 1000 lethal doses, and we find again a quite similar course of the curve. It is interesting to see, however, that the maximum of the curve, which is reached in 5 days, now is only about one half of the maximum obtained after the first injection with one tenth of the amount of toxin.

Figs. 6a and 6b give the details in the two negative phases. In both the minimum is reached after one hour, but they differ in the abruptness of the fall. Then there comes a gradual but pronounced increase that continues in the steep rise of the second phase.

This course of the antitoxin curve was reproduced in 8 other rabbits after active immunization, without any fundamental deviation from the course of the curve here described.

In some other experiments we then tried whether intravenous injection of formol-toxoid might produce similar changes in the antitoxin curve for actively immunized rabbits.

Fig. 7 shows the curve from a rabbit after active immunization, first with subcutaneous injection of anatoxin, and next with intravenous injection of toxin. As in the previous experiments, before the experiment proper, it was ascertained that the antibody curve of the rabbit was in the third phase; here, too, the calculated course of this phase is indicated by a stippled line.

Then 5.5 Fl. U. formol-toxoid are injected intravenously, and, as shown in Fig. 7a, this injection has in all essentials the same effect as was obtained with the intravenous injection of toxin in the preceding experiments.

There now appears a distinct negative phase with a fall that reaches its minimum in 15 minutes after the injection. Then the antitoxin curve rises rapidly; already on the second day the observed curve is crossing the calculated falling antitoxin curve, and it continues in a steep rise.

In a similar experiment on another rabbit the injection of formol-toxoid was repeated, and showed a distinct third phase of the usual character.

Thus the three phases can be reproduced distinctly by intravenous injection of antigen—no matter whether it be formol-toxoid or toxin—in actively immunized rabbits.

If, however, we are to analyse more closely the cause of producing the three phases on the basis of the experiments here reported, we are faced by the difficulty that the obtained variations of the curve are the result of an interaction of several factors, some of which tend to increase, others to reduce, the antibody content of the blood.

Thus the second phase results from the antibody production of the organism, which in turn is counteracted by a concurrent antibody destruction or elimination that finally becomes the predominating

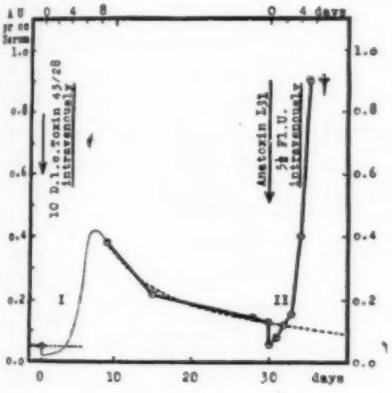


FIG. 7

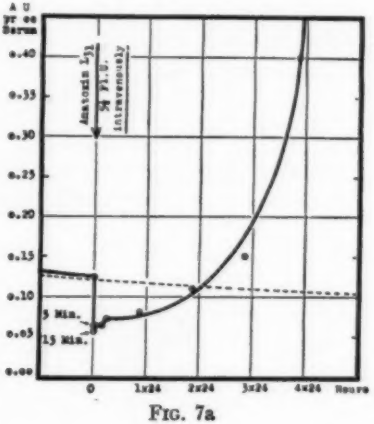


FIG. 7a

factor at the commencement of the third phase, so that the curve is falling off from now on.

EFFECT OF ANTIGEN ON PASSIVELY IMMUNIZED ANIMALS

The antibody-producing factor may be eliminated, however, by employment of passively immunized animals. Experience shows that the rapid and transitory stimulus—of a single *intravenous* injection of antigen in a non-immunized animal—is not able to induce any production of antitoxin worth mention. Only *subcutaneous* injection of antigen, with its protracted effect, is able to immunize such an animal actively.

By repeating the experiments just described on passively immunized

animals it should then be possible to obtain practically phases 1 and 3 alone, the second phase being ruled out under these conditions.

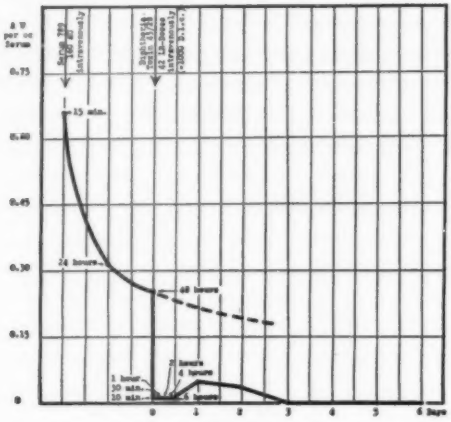


FIG. 8

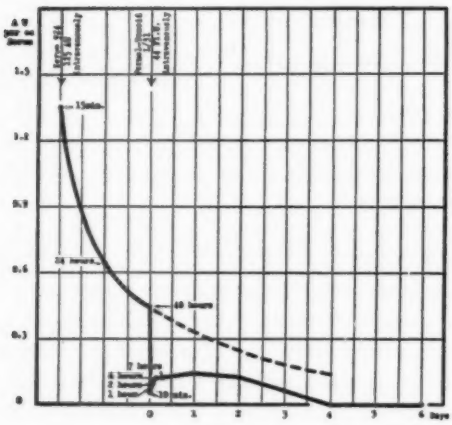


FIG. 9

The following experiments were carried out on 9 rabbits that were immunized passively by intravenous injection of horse serum or rabbit serum with different antitoxin concentration. Then, at cer-

tain intervals, blood was withdrawn for antitoxin titration in order to establish, just as before, some points on the falling curve, after which the further course of the curve was calculated according to the aforementioned formula.

Figs. 8 and 9 show the course of the passive immunization curve before and after intravenous injection of toxin and formol-toxoid, respectively. In these two experiments the doses of toxin and formol-toxoid are fairly alike (42 Lf doses and 44 Lf doses), and the antitoxin concentration of the serum in the two rabbits is of practically the same titer. The curves take an almost identical course: a typical negative phase immediately after the injection, then a slight rise of the antitoxin curve during the next two days, followed by a pronounced fall.

This experiment was repeated on 7 other rabbits, and gave exactly the same course of the curve—no matter whether toxin or formol-toxoid was employed to produce the negative phase.

DISCUSSION OF THE ORIGIN OF THE PHASES

The experiences gained through the two series of experiments on actively and passively immunized animals are now to be utilized for a more thorough discussion of the origin of the three phases. At the same time I shall mention some additional experiments carried out in the State Serum Institute in order to throw some light on the problems brought forth by such considerations.

The negative phase will be dealt with more thoroughly, since its origin has given rise to more discussion. It will be appropriate briefly to mention some of the views on this question that have been advanced previously.

From their experiments with subcutaneous injections of diphtheria toxin, Ramon and collaborators (1929) are inclined to reckon the negative phase as an unspecific phenomenon due to a *tendency to oedema-formation* at the site of injection, causing antitoxin-containing plasma to pass from the blood stream out into the tissues. Furthermore, these investigators were able to produce antitoxin-containing oedemas by injection of such non-specific substances as formalin and tapioca.

Even though we cannot exclude the possibility that diphtheria toxin, which is decidedly a capillary poison, may be able to bring about certain shiftings in

the water distribution of the body, we have to maintain that such a shifting can give only relatively small changes in the antitoxin curve. The prerequisite of this is the formation of a very considerable oedema which may conceivably take place only after subcutaneous injection of the toxin.

Ramon claims, it is true, that the negative phase after intravenous injection of diphtheria toxin may be explained in another way, as horses are said within a few hours after the injection of toxin to show a distinct congestion of the organs, especially the liver. The mechanism of the phenomenon is thought to be an increased permeability of the capillaries, allowing the antitoxin to leave the blood stream.

In order to settle this question about the influence of non-specific factors upon the antitoxin curve, I shall just in passing mention some experiments we have carried out to obtain a numerical expression for marked changes in the amount of circulating blood that may be induced by injection of a large dose of toxin.

An excellent method for estimation of changes in the volume of circulating blood within a fairly short period is to measure the possible shiftings in its hæmoglobin concentration. As here we are interested in the relative shiftings rather than absolute amounts, the examination is made most easily by pipetting off the specimens of blood into equal volumes of diluting fluid. By taking a hæmolyzing diluting fluid, for example, a slightly alkaline salt solution, we may obtain an indication of the varying haemoglobin concentrations of the blood by comparing the color of these hæmolized blood dilutions in a colorimeter. A weaker color will then indicate that the blood has been diluted, while a stronger color means a concentration of the blood resulting from extravasation of fluid from the blood stream.

We have carried out such measurings of the relative hæmoglobin concentration after injection of toxin on immunized and on normal animals, and we found that the toxin gives rise to a certain dilution of the blood after the injection. But even with large doses of toxin—up to 2000 d.l.c., intravenously—this dilution of the blood is only of brief duration (about 1 hour), and amounts to 10–15%, and it has never been possible to demonstrate any concentration of the blood as a sign of extravasation of plasma from the blood stream.

As is evident from preceding curves, the fall in the antitoxin concentration of the blood in the negative phase amounts to 50% or more and lasts a relatively long time (1–2 days); and this fact excludes the possibility that the negative phase may be due to fluid dilution alone. For it is not likely at all that any antitoxin might leave the blood stream without fluid being given off from the blood at the same time, since we know that antitoxin is bound to the most highly molecular proteins of the plasma.

In our experiments in which antigen is invariably injected *intravenously* the question of fluid shiftings will hardly play any rôle, and we shall therefore try to find out whether a more obvious explanation of the origin of the negative phase may tally with our experimental

results. The most probable one will be that the fall in the antitoxin curve takes place, as *in vitro*, *when the injected antigen binds the corresponding amount of the circulating antitoxin.*

This explanation is suggested primarily by the fact that the negative phase makes its appearance at once, immediately after the antigen injection. But in order to substantiate this fixation theory still further, the following two characteristics of the negative phase are essential:

(1) The time required by the antitoxin curve to reach its minimum must show a definite relation to the *fixation time* between toxin and antitoxin *in vitro*.

(2) The extent of the fall—*i.e.*, the loss of antitoxin—must be proportional or equal to the *amount of antitoxin fixed in vitro* by the injected antigen.

(1) The question about the *fixation time* could be examined in our experiments on passively immunized rabbits, as we have used sera of *different avidity* for the passive immunization. This avidity is expressed numerically by the sign *Kf*—the time from the addition of antitoxin to the first flocculation in Ramon titration *in vitro*.

FIG. 10

SERUM USED FOR IMM.		TIME INTERVAL BETWEEN ANTIGEN INJECTION AND MINIMUM OF AT-CURVE
Number	*Kf*	
Antigen injected: Diphtheria *toxin*		
K 717	instantaneous	10 minutes
924	10 minutes	10 minutes
788	1 hour	1–2 hours
1039	5 hours	3 hours
789	6¾ hours	5 hours
Antigen injected: Diphtheria-*toxoid*		
K 717	instantaneous	10 minutes
924	10 minutes	10 minutes
788	1 hour	1–2 hours
1039	5 hours	3 hours

In Fig. 10 the table gives a comparison between *Kf* and the time required for the negative phase to reach its minimum in the rabbit which is immunized passively with the serum concerned. It is quite

obvious that there is a direct proportionality between these two values.

That there is a definite relation between the fixation time *in vitro* and the toxin-antitoxin reactions *in vivo* is evident also from some other work by Th. Madsen and S. Schmidt, which shows that the curative effect of an antidiphtheric serum is largely dependent on its avidity *in vitro*. When two sera are used that differ in their fixation time but show the same content of antitoxin units *in vitro*, a far greater protective effect is obtained with the quickly reacting serum than with the slowly reacting type.

It has further been possible in these experiments to demonstrate the similarity in relation between the duration of the negative pH phase and the reaction time *in vitro*; and this suggests very strongly that the negative phase is brought about through fixation between the antigen and the circulating antitoxin.

(2) The other problem that has to be investigated before this explanation of the negative phase may be accepted, is *that the amount of antitoxin withdrawn from the circulation corresponds to the amount that is fixed in vitro by the injected dose of antigen.*

The amount of antitoxin that disappears from the blood stream in the negative phase may be calculated when the following values are known: the antitoxin concentration of the blood before and after the injection of antigen, and the amount of circulating serum. As already mentioned, the first two values are estimated by the intracutaneous rabbit method. The amount of circulating serum is somewhat more difficult to estimate. Various physiologists have stated, however, that the amount or blood in rabbits may be calculated approximately as 1/20 of the body weight; accordingly, the amount of serum would be 1/30 of the body weight. We have been able to verify the correctness of this figure by determining the antitoxin concentration of the blood after intravenous injection of a given amount of antitoxin in passive immunization of rabbits.

Example: Rabbit no. 1497 is given 150 antitoxin units intravenously. 15 minutes later the antitoxin concentration is 1.25 units per cc. of serum.

Thus the amount of serum is 150 : 1.25 = 120 cc.
The animal weighed 3500 gms.
1/30 of the body weight = 116 cc.

As can be seen, the two methods of calculation give about the same values, and in the following calculations we shall not make any great errors by setting the *circulating serum volume = 1/30 bodyweight.*[8]

FIG. 11

ANTIGEN	METHOD USED FOR IMMUNIZATION	RATIO: AT IN VIVO / AT IN VITRO	MEAN
Toxin	Active	1.8 3.2 2.2 1.4 1.6 3.0 2.5 2.5 1.3	2.17
Toxin	Passive	1.3 2.6 1.6 2.0 1.5	1.80
Toxoid	Active	1.07 1.33	1.20
Toxoid	Passive	1.4 1.0 0.82	1.07

Fig. 11 gives a tabulation and calculation of the ratio between the loss of antitoxin from the blood stream and the amount of antitoxin fixed by the same dose of antigen *in vitro*.

From these findings it is evident: (1) There is a constant relation between the loss of antitoxin in the rabbit and the amount of antitoxin fixed by the injected antigen *in vitro*. (2) In experiments *with injection of toxin this ratio comes very close to 2; with injection of formoltoxoid the ratio is equal to 1.*

[8] Erin Madsen has adopted this principle for elaboration of a method to determine the amount of blood in man by means of diphtheria antitoxin. (*Dissertation*. Copenhagen, 1936.)

This difference in the effects of toxin and formol-toxoid *in vivo* ought to attract attention, and further experiments of this kind are desirable.

The deviations from these averages fall inside the limits of experimental errors. It is understood, of course, that a little error of measuring in the determination of the antitoxin concentration of the serum in these calculations will be multiplied by the not altogether certain value for the amount of serum, so that it becomes justifiable to draw conclusions from such experiments only when the method employed is fully reliable and adequate for demonstration of slight variations in the antitoxin concentration. This explains why previous determinations after the old guinea-pig method cannot be expected to give approximately the same results as are presented here.

In view of this indisputable resemblance between antitoxin-toxin reactions *in vitro* and the phenomena we have found associated with the negative phase, we feel fully justified in claiming that ***the negative phase results from fixation between antigen and antitoxin in the blood stream.***

Thus we have been able to demonstrate that the negative phase is due to a binding between antigen and antitoxin. But now—*How about the further fate in the organism of this antigen-antitoxin complex?*

As mentioned before and demonstrated in the curves here presented, within a few hours the negative phase turns into a slow increase of the antitoxin curve, and in active immunization this turns into the rapid rise of the second phase. The moderate, early-appearing, increase immediately after the fall is also observed in the curves from *passively* immunized rabbits (see figs. 8 and 9).

As intravenous injection of antigen in the case of passively immunized organisms does not give rise to antibody production, the rapidly appearing initial increase after the negative phase in such organisms can not therefore be explained as a beginning production of antitoxin. There are different possibilities of explaining this phenomenon:

(1) Antitoxin is mobilized from possible *depots* in the organism outside the blood stream.

(2) The new-formed antitoxin-antigen complex is dissociated and the antibody liberated.

(3) The immunizing power of the diphtheria toxin is different from the antitoxin fixing power.

(It is usual to adopt the Ehrlich view, that the antitoxin-fixing part of the diphtheria toxin should be identical with its immunizing power, but it might be useful to include in our discussion a different point of view.)

(1) The first assumption presupposes that depots of antitoxin would be formed both in the actively and in the passively immunized organisms. This is rather difficult to imagine in the case of the passively immunized organism, because the antitoxin completely disappears gradually according to the aforementioned law, and it cannot be demonstrated later on.

Experimental studies of this point have been carried out by Buttle on actively immunized rabbits, and his findings appear to be against the existence of such rapidly mobilizable depots.

In actively immunized rabbits, Buttle tries to draw off the greater part of the animal's blood by fractional bleeding and perfusion of the circulatory system with blood from normal rabbits. In the course of this perfusion, the circulatory system of the rabbit is passed through by twice the volume of blood originally present in this rabbit. Yet Buttle is unable to demonstrate any more antitoxin in the evacuated amount of blood than was found in the animal's own evacuated blood.

If this actively immunized animal had possessed any depots of antitoxin that could be mobilized readily, they would most likely have given off some antitoxin to the non-antitoxin-containing blood with which the circulatory system of the animal was flooded.

So the question of a depot effect as the cause of the immediate increase in the antitoxin concentration after the negative phase will have to be regarded so far as rather improbable.

(2) On the other hand, there is every reason to assume that this little increase is due to a liberation of the antitoxin that was fixed by the injected antigen.

This brings us back to the old question *whether the complex of diphtheria toxin-antitoxin is dissociable.* As you know, Ehrlich claimed that the combination of these two substances was something like that between a strong acid and a strong base, whereas Arrhenius and Madsen asserted that this curve is very like that which represents the

equilibrium between a body in partial dissociation and its products of dissociation:

$$\left(\frac{\text{Free toxin}}{\text{vol.}}\right)\left(\frac{\text{Free antitoxin}}{\text{vol.}}\right) = K\left(\frac{\text{Combined toxin-antitoxin}}{\text{vol.}}\right)^2$$

From the lengthy discussion in those days concerning this question, no doubt, it was evident that our point of view was the more correct. Besides ourselves, several other investigators were also able to show that *in vitro* the complex could dissociate into its components (Morgenroth, v. Krogh, Ramon, and others). Madsen and Schmidt[9] have pointed out the important rôle which the avidity of the components play in the stability of the complex.

That a dissociation takes place *in vivo* too, is something we are almost bound to presume in order to explain how an antigen may have a stimulating effect upon the antitoxin production in an actively immunized organism, after it has been neutralized in excess by antibody.

When two days elapse before the strong increase in the second phase appears, the most reasonable explanation of this fact will be that it takes this length of time before the antitoxin-producing cells can respond to the effect of the liberated antigen by production of antitoxin.

The antitoxin-antigen complex which is formed during the negative phase must be assumed during this dissociation to keep on circulating in the blood stream. This is evident from the following experiments which we have performed on a series of *actively* immunized rabbits:

Expt. 1. One of the rabbits (A) was given a dose of toxin intravenously. After 10 minutes about $\frac{1}{4}$ of its total amount of blood was evacuated through an arterial cannula, and this blood was transfused into another actively immunized rabbit (B) from which $\frac{1}{4}$ of its blood had been withdrawn immediately before. A sample of the transfused blood showed it contained a great excess of antitoxin.

Rabbit A simultaneously got its loss of blood covered by transfusion from a fresh rabbit.

[9] Madsen and Schmidt: *l. c.*

After 4 days both rabbits (A and B) showed a strong rise in antitoxin concentration, indicating that the neutralized antigen from rabbit A had become free again, and that it must have been present in the blood in the intervening period.

Fig. 12a shows the details in the antitoxin curve of rabbit B.

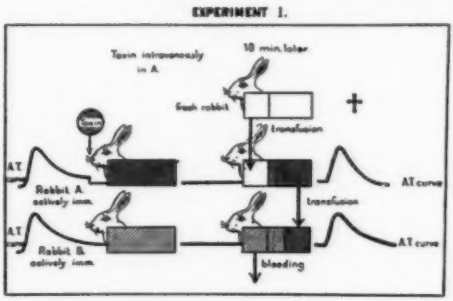


FIG. 12

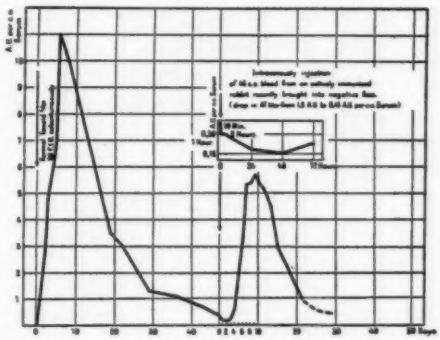


FIG. 12a

Expt. 2. When this experiment was repeated by injecting the toxin into a *passively* immunized rabbit (A) and $\frac{1}{4}$ of its blood was transfused into an actively immunized rabbit (B) there appeared a rise in the antitoxin concentration only in the actively immunized animal, whereas the passively immunized animal in the following days showed the usual fall in the antitoxin concentration.

In Fig. 13a are indicated the details of the antitoxin curve of rabbit B. In them are magnified the details of the negative phase observed after the injection of the blood from rabbit A.

These considerations and experiments all lead on to the view: that the rapidly appearing increase in the antitoxin curve after the nega-

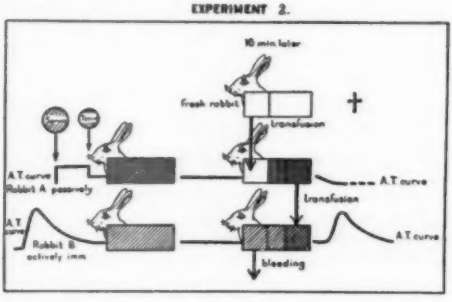


FIG. 13

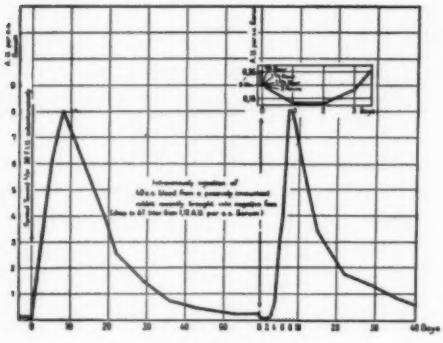


FIG. 13a

tive phase in passively and actively immunized rabbits is due to a liberation of antigen from a toxin-antitoxin complex circulating in the blood stream.

The liberated antigen therefore tends to stimulate the antibody-producing factors of the organism. Whether this will bring about a rapid and considerable antibody production depends on whether these

organs or cells have already been stimulated beforehand. In the *passively* immunized organism the liberated antigen acts merely as a *primary* stimulus, hence it gives only a very slight antitoxin production that is very late in its appearance.

In the *actively* immunized organism, on the other hand, the antigen acts as a *secondary* stimulus, inducing a quick and considerable antitoxin production.

As far as I know Rufus Cole was the first to demonstrate the remarkable impression which an antigen injection leaves in an actively immunized organism.

THE SECOND PHASE

Now let us consider the *ascending part of the curve*—that phase in which the antitoxin production after a single injection of toxin manifests itself most distinctly. Here we must realize that the destructive factor also is asserting itself right along, and we have to assume that production and destruction are counter-balancing each other when the curve is at its maximum. Looking on different curves, one gets the impression that the production at first proceeds somewhat slowly, but then increases rather rapidly till it reaches a maximum, whereafter it falls off abruptly. We shall also have to reckon that some antitoxin production is still going on in the beginning of the fall in the 3rd phase.

Supposing that the breaking-down of the antitoxin in the organism is continually taking place in the same manner as in the 3rd phase we are able from the experiment in Fig. 6 to construct the following curve for the rate of antitoxin production.

This figure shows graphically that the production reaches a maximum on the 4th to 6th day, after which it falls off.

In *conclusion* I should like to mention a comprehensive experiment that elucidates this second, productive, phase and shows that the more "productive" the organism is adjusted to be, the more rapidly the antigen injection is followed by antibody production.

Rabbit 67 was actively immunized by subcutaneous injection of formol-toxoid and by an intravenous injection of toxin. The latter injection was followed by the three phases in a regular manner. At

this point the experiment proper was performed, late in the third phase. The corresponding antitoxin curve is shown in Fig. 15.

The animal is given 100 d.l.m. of toxin intravenously. This produces a normal negative phase (I), after which the curve begins to rise slowly; on the third day the second phase sets in with a steep rise.

While the antitoxin production is still in the beginning of the second phase the animal is again given an intravenous injection of toxin (1000 d.l.m.) (II). There ensues a negative phase, but the antitoxin production, which is now going on in full swing, keeps on unhampered, for we find a steep rise in the curve on the next day already.

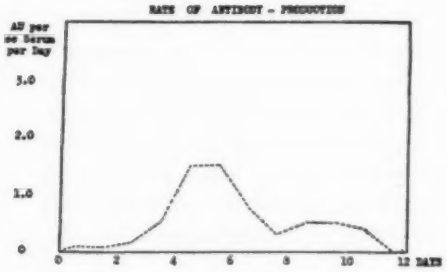


FIG. 14

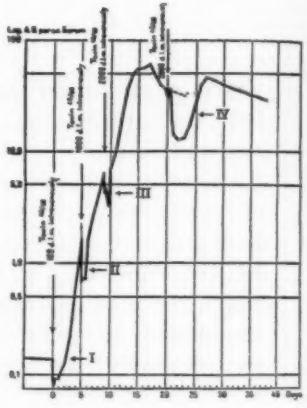


FIG. 15

While the curve is still ascending, the animal is again (III) given a new injection of 2000 d.l.m. of toxin, with exactly the same result as before: The curve rises abruptly on the day after the negative phase, indicating a strong antibody production. This now keeps on up to the maximum, after which the curve begins to fall off, as the continual loss of antibody which goes on in the organism overcomes the decreasing production.

Two days after the maximum of the antitoxin curve the animal is again given a dose of toxin (2000 d.l.m.). But this time (IV) the curve takes a quite different course. The negative phase continues during the following days, and not until the 7th day after the antigen iniec-

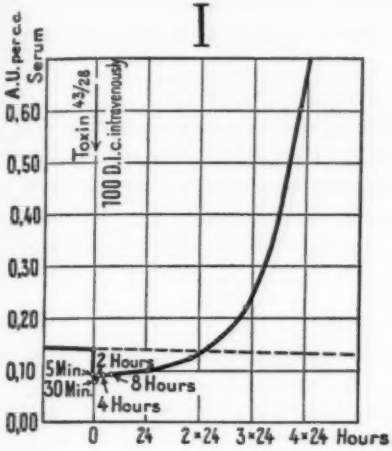


FIG. 15a

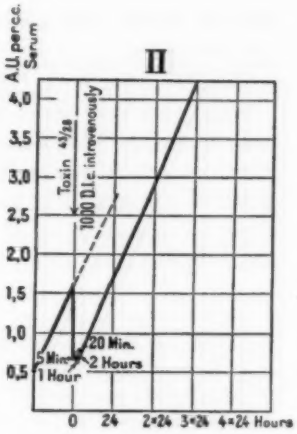


FIG. 15b

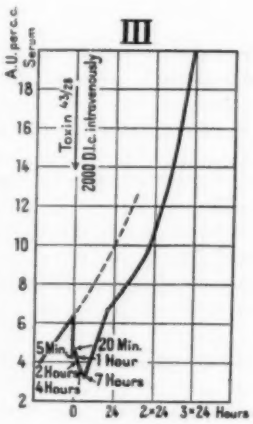


FIG. 15c

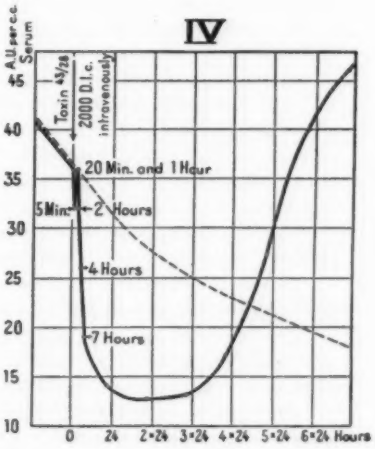


FIG. 15d

tion is there a rise in the curve due to the renewal of the antitoxin production, which stops again after a couple of days, and the curve falls off once more.

The details of I, II, III and IV are in Figs. 15 a–d.

After this experiment it seems fully justifiable to assume that the reason why the 2nd phase ceases and turns into the 3rd phase must be: that the antitoxin-producing factors, so to speak, are getting exhausted and are beginning to be overcome by the antibody-destructing factors. Hence a new stimulus of antigen is only able to induce a late and scanty production of antibody.

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A CASE OF EXTENSIVE INJURY TO THE CEREBRAL CORTEX FOLLOWING NITROUS OXIDE-ETHER ANESTHESIA

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The following case[1] is reported for two reasons. First, because it illustrates the possibility of grave injury to the brain during general anesthesia produced by nitrous oxide and tends to confirm the conclusions of Courville and of Löwenberg in this regard. Secondly, because we wish to present a series of very interesting neurological disorders which the patient exhibited and which we believe point to extensive destruction in the occipital and parietal cortex on both sides, in the cortex of the cerebellum and in the lenticular nuclei. Few cases of this type have been subjected to a careful neurological study and the symptoms have often been briefly dismissed as indicating dementia. We wish to show that the patient's symptoms were not general but were selective and that the apparent dementia was associated with a large number of focal signs and symptoms.

CASE HISTORY

A healthy young man of 33 years was operated upon for bilateral herniae under nitrous oxide and ether anesthesia. During the operation respiration failed. He was resuscitated but developed convulsions and remained in coma for 36 hours. Subsequently there was bilateral apraxia, aphasia, reduction of vision, loss of visual fixation and moderately severe cerebellar ataxia. The aphasia and apraxia disappeared after several weeks but the ataxia and reduction of vision persisted for more than 6 months.

[1] We wish to thank Dr. T. R. Boggs for permission to publish this case.

J. C., a colored laborer of 33 years, was operated upon on September 5, 1936, for the repair of bilateral inguinal herniae. He had no complaints referable to the herniae but wished them repaired because his employer threatened to discharge him unless he submitted to operation. His health had always been good and he could recall no serious illnesses. There was no history of venereal disease. The patient had received little education and had stopped school to go to work when in the second grade. He had not learned to write or to read easily but knew his alphabet and could recognize short and common words. He could understand figures fairly well and could make simple calculations. Physical examination was quite negative except for the presence of the herniae. The Wassermann reaction was negative.

Operation was begun under spinal anesthesia, 150 milligrams of novocain being injected. The anesthesia was satisfactory for a time but passed off before the operation was completed. Nitrous oxide and ether were then administered and a quarter of a grain of morphine was injected. Shortly after the inhalation anesthesia was begun the patient stopped breathing. Artificial respiration was carried on for about ten minutes after which spontaneous respiration was reestablished. The pulse was always satisfactory. The operation was then completed without further incident.

After his return to the ward, the patient remained in a state of coma for 36 hours. During this period he had several convulsive seizures which are said to have been generalized. His head and eyes turned to the left during these seizures. His temperature reached 102.8°F. on the third day and then slowly fell to normal on the eighth day. The pulse curve paralleled the temperature curve. The blood pressure remained unchanged, averaging 118/88. Signs of returning consciousness were noted at the end of 36 hours and another 36 hours passed before the patient seemed fully conscious. The convulsions were not observed after the first day. The wound healed by first intention.

On the third day after operation the patient was in fairly good contact. He was, however, unable to express himself clearly and did not seem to understand what was said to him. He could move all four extremities, the face was symmetrical and he could swallow but could not feed himself. He appeared to be blind but his pupils reacted promptly to light. The optic discs and retinae were normal. The tendon reflexes were active and equal on the two sides and the plantar reactions were normal.

On the fourth day, the patient was conscious and cooperative. It was difficult to understand what he wished to say, for he frequently employed words which were evidently unsuitable for his meaning. His sentences were imperfectly formed but his articulation was fairly clear. He had great difficulty in understanding what was said to him. If asked to touch his nose, he appeared to be completely puzzled. If the examiner grasped his hand and showed him what was desired, he would make an effort to comply, but even the simplest acts were imperfectly performed. As a rule he merely flourished his arms around at random. It was impossible for him to take a match out of its box, to strike it or to light a

cigarette. He could not place a cigarette in his mouth nor could he take a drink of water when the glass was put into his hand. There was no demonstrable weakness of the extremities and no obvious change in muscle tone on passive movement, but there was mild ataxia in both arms. Vision was greatly affected. It was agreed by all examiners that the patient was not totally blind, but it was impossible to determine how much vision he possessed. He showed no evidence of recognizing familiar objects. There was a striking inability to fix objects with the eyes. After repeated requests to look at an object had finally made the idea clear to him, he would turn his eyes in almost any direction except the one desired. Even when the test object was placed in his own hand he could not fix it properly. Ophthalmoscopic examination showed normal media and sharply outlined optic discs. There was possibly a little hyperemia of the discs and the veins were possibly a trifle dilated, but these changes were not beyond normal limits. The maculae and peripheral portions of the retinae were quite normal. The pupils reacted well to light. It was evident, therefore, that the patient was suffering from aphasia, bilateral apraxia, mild ataxia and from some profound disorder of the visual functions.

During the next two weeks he improved slowly in his speech and in his ability to understand what was said to him. He also acquired some control of his arms so that he could carry a cup to his lips, although with considerable difficulty.

On September 28, some twenty days after the operation, a more complete examination was performed. Examination of the eyes showed no ptosis or squint. The ocular movements were of full range and there was no nystagmus. The pupils were round, equal, and reacted promptly to light both directly and consensually. Visual acuity could not be estimated accurately. The ophthalmoscopic picture was unchanged. There was no demonstrable disorder of the fifth, seventh, eighth, ninth, tenth, eleventh or twelfth nerves. The musculature was firm and strength was excellent. On passive movement no definite change in muscle tone was evident. Tests of coordination were made with difficulty because of the apraxia, but there was clearly some ataxia of both arms which was associated with a mild intention tremor. There was no tremor of rest. Similar ataxia was present in the legs. The patient stood and walked unsteadily and the gait was typical of cerebellar ataxia. Articulation was distinct. There was no disturbance of sphincter control. Sensibility was tested with difficulty. It was clear, however, that the patient could feel touch, pain, warm and cold. Subsequently it was possible to show that sense of passive movement, sense of position, vibration and two-point sense were preserved. The tendon reflexes were all active and equal on the two sides. Plantar reflexes were normal. The abdominal reflexes were equal.

There was gradual improvement in the patient's condition and during the second month of the illness it was possible to make a series of special tests which are described below:

Motor Speech: Articulation was never severely affected and within a few days after the operation the patient could form short sentences. It was difficult for him to make himself understood, however, for he frequently failed to find the words

he wished to use and was also prone to employ words which were not suitable for his meaning. His mistakes were most often due to repeating words used in the preceding sentence, *i.e.* perseveration.

Understanding of Spoken Speech: The patient could understand little or nothing of what was said to him during the first few days of the illness. Within a month, however, he could understand short sentences and would carry out a single request to the best of his ability. Two requests within a single sentence were beyond his grasp until the end of the second month.

Anomia: During the first few weeks of the illness the patient was unable to name objects correctly. Even at the end of the second month, he made many errors in this regard. To a certain extent this symptom was due to failure to to recognize the object, but on numerous occasions we were able to satisfy ourselves that he recognized objects that he could not name.

Agnosia: We could never be certain about the presence or absence of tactile agnosia. The difficulties in visual fixation and attention and the gross reduction of central vision made it impossible to detect visual agnosia.

Apraxia: The patient displayed bilateral apraxia for at least a month after the operation. He could not feed himself, could not light a match and could not even convey objects to his mouth. This was not due to ataxia which was always mild. At the end of the fifth week he could dress himself, though he was very slow and uncertain. At the end of two months he could carry out on request such simple movements as shaking his fist, waving 'goodby,' combing his hair, brushing his teeth and winding up a victrola with and without the appropriate test object. He was still slow and uncertain and sometimes repeated the movement made in the preceding test.

Vision: The existence of aphasia and of apraxia made it impossible to gain any clear idea of the patient's visual acuity during the first few weeks of his illness. At the end of the second month, however, these difficulties had disappeared to such an extent that we were able to determine that vision in the right eye was about 10/200, and in the left eye about 20/200. Retinoscopy revealed emmetropia. The outlines of the visual fields tested with a one degree disc were normal but an homonymous scotoma was found in each of the left inferior quadrants which extended into the fixation points. Great difficulty was encountered in testing the visual fields, for the patient seemed to have little or no power of fixation or of attention and it was only after repeated tests had been made during a period of six months that we were quite sure that the preceding statements were correct. It was evident, therefore, that the patient exhibited disorders of vision which could not be explained by the reduction of visual acuity or by the presence of the scotomas. In attempting to discover the nature of these disorders we have compared the patient with others suffering from retrobulbar neuritis who had central scotomas of comparable size and intensity.

Visual Attention: The patient rarely noticed what was going on around him and would not direct his eyes towards the examiner during conversation. He frequently walked into objects in his path, although his vision was adequate for

him to see them across the room. If two objects were held up before him he never saw more than one even when told that there was another object in his field of vision.

Recognition of Movement: He could usually, but not always, tell whether a test object was moving upward, downward or laterally, but rarely could say whether it was coming closer to him or going away. This symptom was present at the end of the first month but disappeared shortly afterwards.

Reading: The patient was never able to read. Since vision was much reduced and he had never learned to read well, it is impossible to lay any stress on this, but we are inclined to believe that here there was also a certain degree of alexia.

Writing: The patient had learned to write his name in school but was never able to produce a recognizable signature or even to copy letters or figures.

Volitional Ocular Movements: Spontaneous ocular movements were of full range and there was never any tendency to conjugate deviation. He would sometimes move his eyes to the right when requested to look to the left, but this was probably due to difficulty in understanding.

Ocular Fixation: One of the most striking symptoms which the patient displayed was complete inability to fix test objects with his eyes. During the first two months he could never maintain his gaze upon test objects even when they were clearly visible to him. Moving objects attracted his attention more readily than stationary objects but he could not follow them with his eyes. He did not fix his own hand any better than any other test object.

Optic Nystagmus: During the first two months of the illness, we were unable to discover any evidence of optic nystagmus by the use of the revolving drum. At the end of six months, however, active nystagmus was produced with ease and the study of the ocular movements by photographic methods showed that this nystagmus was quite normal.

Projection of Objects in the Visual Fields: The patient could not point directly at a test object held before his eyes in either central or peripheral fields. He made many gross errors in the horizontal and vertical planes. These symptoms slowly diminished but were present at the end of the second month.

Binocular Vision and Depth Perception: A study of fusion ability and depth perception was made throughout the course of our observations. These studies may be summarized as follows: During the first two months, he seemed to have some loss of depth perception. If two test objects, which he could see with either eye, were held within his range of vision, he had great difficulty in stating which was the closer and could do so only when the objects were at least two feet apart and the further object was not more than ten feet away. Studies with the hand stereoscope gave inconclusive results. It seemed that he had some degree of binocular vision but the difficulties in visual fixation, in attention and in visual acuity made it impossible to secure consistent results. After six months, however, examinations were made with greater ease. Although his visual acuity had not improved definitely, ocular fixation was much better and induced optic nystagmus was easily elicited. He was found to have binocular vision and fusion as deter-

mined with the hand stereoscope, Worth's four-dot test and the synoptophore. Gross tests indicated that he had depth perception and this was confirmed by tests on the stereo-orthopter. Although at the end of the sixth month the patient was found to have binocular vision with stereopsis, no conclusions could be drawn as to the presence or absence of these functions during the early months of the illness.

Memory of Topography: As soon as the patient began to walk, it was evident that he had difficulty in finding his bed, for he would frequently turn in the wrong direction and get lost. When in bed with his eyes closed he could not point to the table, the chair or the window. These symptoms disappeared within five weeks.

Projection of Sounds: The patient could always localize sounds correctly.

Mental Status: The patient's behavior was always good. He was cooperative throughout the entire course of his illness. His manner was pleasant. There was never any evidence of emotional instability, of irritability or of impatience. He was, however, very apathetic and would sit for hours without appearing to take any notice of the activities of the patients or nurses about him. When addressed, he invariably responded at once. His talk was always relevant. We could never discover any delusions or hallucinations. He was oriented for the year and usually for the month but never knew the day of the week or month. He knew he was in a hospital but never retained the name of the hospital or those of the examiners whom he saw almost every day. He could not recall what he had eaten for recent meals. Remote memory was very good. His fund of information was consistent with his education. Calculation was poor but probably up to his usual standard. He could perform simple addition and subtraction so long as the numbers were small. He could retain five digits and repeat them in the order given but could not repeat three digits backwards. He recalled only one of four test objects. His attention diminished very rapidly during the examination and he was easily confused. After failing on a test he would make many mistakes in tests he had been able to perform before.

Course of the illness: At the end of the second month, it was discovered that a mild cog-wheel rigidity was present at the wrist on passive movement when the patient's attention was distracted. If this sign was present before, it was not discovered. If his attention were not distracted when the test was made, passive movement revealed no increase of tone. In fact, tone seemed to be diminished. There was no tendency to masklike face, no tremor of rest, no loss of arm swing or any other sign of the Parkinsonian syndrome. Definite cerebellar ataxia was still present. There was mild ataxia in the extremities and the gait was typical of cerebellar disease. At this time he had so far recovered from the aphasia as to be able to express himself in a comprehensible manner and to understand simple directions easily. He could sometimes grasp two orders included in one sentence but failed invariably only when three orders were given at once. His apraxia had disappeared almost completely, for he could wash, dress, and feed himself and could perform all the usual tests with few errors. He was slow and uncertain, however, and would occasionally repeat the movement of the preceding test.

Visual acuity was estimated to be 10/200 in the right eye, and 20/200 in the left eye. There was a homonymous scotoma in the left lower quadrants which involved the fixation point. Ocular fixation was almost entirely lost and it was impossible to induce optic nystagmus with the revolving drum. He still had some difficulty in projecting objects in the visual fields. Memory of topography was much better and he could find his way around the ward.

At the end of the sixth month the patient was reexamined. He seemed to have made a complete recovery from the aphasia, for he never hesitated for a word and could always carry out two orders given together, and frequently grasped three orders in one sentence. There was no apraxia, for the patient could go through the whole series of tests with facility and accuracy. Visual acuity had not improved and was still 10/200 in the right eye and 20/300 in the left eye. The scotomas in the left lower quadrants were still present and of about the same size. The optic discs and retinae were still of normal appearance. The power of visual attention, of projection, and of fixation were improved but not normal. Optic nystagmus was now easily elicited with the drum. The cog-wheel rigidity had disappeared completely but the cerebellar ataxia was still present. His gait seemed to be improved but was still definitely ataxic. His mental status was improved. He was more alert and active. Memory for recent events was better and he could concentrate better during the examination. He was fully oriented.

Discussion of the Neurological Symptoms: We shall now consider the chief symptoms and try to correlate them with the probable site of the lesions in the nervous system.

The patient's vision was markedly reduced but there was never any alteration of the optic discs and the pupillary reflexes were always active. It seems evident therefore that the reduction of vision was of central origin and due to lesions in both optic radiations or in the visual cortices of both occipital lobes. The prolonged loss of optic (induced) nystagmus is a feature of great interest. It is believed that nystagmus of this type is dependent upon reflexes which are subserved by efferent pathways arising in the occipital lobes and ending in the brain stem where they form connections with the nuclei of the extra-ocular muscles. The afferent pathway is probably closely connected with the visual pathways. Optic nystagmus is never permanently abolished, in our experience, by unilateral lesions in the cerebral hemispheres. Lesions in both occipital lobes might well be responsible for the loss of optic nystagmus. The inability to fix moving objects is merely another manifestation of the same loss of function which was shown by the absence of optic nystagmus. In a very interesting series of papers Gordon Holmes has described disorders of

spatial orientation, of visual attention, and of ocular fixation in patients who had gunshot wounds passing through the brain in the region of the supramarginal and angular gyri on both sides. Similar symptoms have also been described in bilateral cortical lesions in the same region. It therefore seems a reasonable supposition that these symptoms in our patient were due to bilateral lesions in the posterior part of the parietal lobes. The apraxia might be easily explained on the same basis for it is well known that, when bilateral apraxia results from one lesion, the lesion is most apt to be found in the region of the supramarginal and angular gyri on the left. The aphasia was chiefly of sensory type and therefore probably a result of injury to the left hemisphere in the temporal or parietal lobe. The persisting ataxia of cerebellar type indicates involvement of some part of the cerebellar system and the transient cog-wheel rigidity of the arms might be correlated with mild injury of the lenticular nuclei.

In summary, therefore, we may say that the symptoms might be explained by bilateral lesions in the cerebral cortex involving the occipital lobes, the posterior part of the parietal lobes, especially the region of the angular and supramarginal gyri, the cortex of the cerebellum, and the lenticular nuclei. It will be discovered in the following pages that these regions of the brain are selectively involved in such cases.

Discussion of Cases in Medical Literature and of the Lesions: In a recent article, Courville called attention to certain cases in which serious lesions in the central nervous system occurred during anesthesia induced by nitrous oxide. His experience included 13 cases and he was able to find 6 cases previously described in medical publications. A brief summary of Courville's paper may be given as follows: The anesthesia was not always prolonged for, in a large percentage of cases, it is stated that the operation lasted only "a few minutes" and it is stated specifically that anesthesia was of only 10 and 12 minutes' duration in two cases. The nature of the operation was apparently not important. Several minor operations were included, such as biopsy, uterine curettage, and extraction of a tooth. In a few cases symptoms, which Courville describes as prodromal, occurred during operation. These included cyanosis and irregularity of respiration. They were sometimes followed by more serious symptoms. In 8

cases there was sudden failure of respiration and in 4 cases the pulse became very feeble or imperceptible. In 4 cases no symptoms whatever were noted during the anesthesia. When the anesthetic was withdrawn the patient always remained in deep coma. There was usually definite elevation of temperature during this period. Respiration was irregular and sometimes of Cheyne-Stokes' character. Convulsions occurred in many cases and were sometimes general and sometimes focal. Generalized muscular rigidity was observed in a large percentage of cases. In some instances the patient died without regaining consciousness, usually within 2 to 7 days. Terminal hyperthermia was common. In other instances, the patient survived and the neurological symptoms rapidly disappeared. Certain patients, however, survived with permanent mental or physical disorders, indicating destructive changes in the nervous system. Mental deterioration seems to have been the most frequent sequel. Disturbances of speech were mentioned and also involuntary laughter, screaming, and weeping. Disorders of vision were observed in several cases, due apparently to cortical lesions. Athetoid movements and Parkinsonian syndromes are mentioned.

The lesions are described very fully. Apparently the most destructive changes were in the cerebral cortex. These were usually diffuse or disseminated. The distribution was not always the same. In some cases the frontal cortex was most severely affected but, as a rule, the occipital lobes were most seriously involved. There were frequently areas of necrosis in the lenticular nuclei, not unlike those seen in carbon monoxide poisoning. The Purkinje cells of the cerebellum were usually involved. The subcortical white matter, the various structures of the brain-stem, the spinal cord, and the peripheral nerves apparently did not suffer. Four types of pathological change were found: (1) Degeneration of individual cells. (2) Small foamy areas of vacuolation and rarefaction of the tissues. (3) Zonal necrosis in the cortex, often destroying certain cortical layers and sparing others. (4) Complete disintegration of the cortex which seemed to be a more advanced stage of zonal necrosis. The small blood vessels supplying the basal ganglia frequently showed deposits of calcium in their walls. In cases in which the patient had survived long enough, there was proliferation of the astrocytes, and phagocytosis of cellular débris by the microglia.

The author discusses the action of nitrous oxide and concludes that, although there is probably some direct narcotic action on the nervous system, its chief action in inducing anesthesia is due to asphyxia. The lesions in the nervous system, he attributes to asphyxia. The possibility that impurities in the gas or faulty methods of administration might play a part in the injury to the nervous system is mentioned. It is also emphasized that obstructions in the respiratory passages, pulmonary diseases, and various other abnormalities in the patient might be important.

Löwenberg *et al.* describe four cases which were almost identical with those of Courville. In three cases the patient died and postmortem examination revealed lesions in the cerebral cortex, lenticular nuclei, and cortex of the cerebellum. The third, fifth, and sixth layers of the cerebral cortex were most severely damaged. One of the three fatal cases was that of a young man of twenty-two years who was under anesthesia only twenty minutes. The operation was a minor one to drain an infected finger. Löwenberg differs from Courville in that he ascribes the injury to the nervous system to a toxic action of the anesthetic rather than to asphyxia.

A few scattered cases are reported in which ether anesthesia has been associated with cerebral symptoms. Hadfield cites a number of cases in which convulsions have occurred following ether anesthesia. No instances were mentioned, however, in which the patient presented persisting symptoms. Hadfield believes that the ether was administered improperly or contained toxic products. Parkes Weber has reported a case in which status epilepticus developed following operation for acute appendicitis under ether anesthesia. Subsequently the child was entirely demented and showed bilateral spastic paralysis. Speech, vision, and indeed, all other functions dependent upon the cerebral cortex were abolished. The child survived in this vegetative state and the nature of the anatomical changes was not determined. One of the writers has also observed a case which was in every way similar to that of Weber, although the cerebral damage was fortunately much less serious. The patient was a healthy boy of 8 years who developed acute appendicitis and was operated upon under ether anesthesia. Shortly after the anesthetic was started he became cyanotic but respiration

did not cease. Later, there were several convulsions and the child was confused or delirious for two weeks or more. Unfortunately, proper neurological studies were not made. Several months after the illness he returned to school but could not make any progress. He had been among the leaders of his class before the operation. Neurological examination was quite negative but it was evident that there was definite reduction of mentality. The child had to be taken from school.

It is well known that spinal anesthesia may occasionally result in injury to the nervous system. We have seen two cases in which the spinal cord was severely injured and meningeal irritation is also described. The total absence of spinal disorders in this case renders it very unlikely that the spinal anesthesia played any significant part in our patient's symptoms.

It is difficult to offer any explanation for the injury to the brain in these cases except to say that it is evidently due in some way to the anesthesia. There is no evidence of preexisting disease of the nervous system in any case. In a large percentage of cases the patient was young and quite healthy except for some local condition requiring operation. There is nothing to indicate that arterio-sclerosis or disease of the cardiorespiratory system is important. The duration of the anesthesia is obviously not significant since, in many cases, the anesthesia was very brief. In eight of Courville's cases there was failure of respiration or of cardiac action during operation, but in four cases no disturbance of respiration or of the pulse was noted. It is evident therefore that this condition may develop in patients who show no clinical evidence of an unusual degree of asphyxia. The writers are inclined to doubt that asphyxia alone is responsible, but would be inclined to attribute the damage to a toxic action of the anesthesia in association with asphyxia. Whether these factors act directly upon the neurons or indirectly by inducing local vasomotor effects is still uncertain. From the current literature on the subject, one gains the impression that nitrous oxide anesthesia is more apt to injure the nervous system than other anesthetics, but further investigation may show that this view is erroneous. Certainly ether anesthesia may be followed by similar symptoms. The hemiplegia which sometimes occurs in elderly subjects with cerebral vascular

disease during the course of anesthesia is probably due to thrombus formation in cerebral arteries and, hence, is not to be confused with the condition under consideration.

SUMMARY

The case of a young man is described who was operated upon for bilateral herniae under nitrous oxide-ether anesthesia. Respiration failed during the operation, but the patient was resuscitated. Consciousness was not regained for 36 hours and, during this period, there were several convulsions. Subsequently the patient showed evidences of severe damage to the brain. There was aphasia of receptive type, bilateral apraxia, reduction of vision of cortical type, loss of visual fixation, of optic nystagmus, of spatial orientation, cerebellar ataxia, and transient cog-wheel rigidity of the extremities. The aphasia and apraxia soon disappeared but the other symptoms were still evident at the end of six months. We have attempted to show that these symptoms may be explained by bilateral lesions in the cerebral cortex involving chiefly the occipital and parietal lobes, the cortex of the cerebellum and the lenticular nuclei.

The writers believe that the injury to the brain was in some manner a result of the anesthesia and that the case was identical with those reported by Courville and by Löwenberg and others. It is pointed out that similar cases have followed ether anesthesia.

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OBSERVATIONS ON THE DEVELOPMENT OF INTRATHORACIC CALCIFICATION IN TUBERCULIN-POSITIVE INFANTS[1]

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When calcification is seen in X-rays of the chest of young children, the finding is usually accepted as objective evidence that a tuberculous process is present and is either healed or beginning to heal. It is the purpose of this paper first to record observations as to the rate at which intrathoracic calcification was first noted in a group of children known to have been infected with tuberculosis before two years of age; and secondly, to present a few points of clinical interest relative to those cases in which calcification was seen to take place.

SOURCE OF MATERIAL

The material for study is derived from the special outpatient clinic for childhood tuberculosis which has been in operation under the direction of Dr. E. A. Park at the Harriet Lane Home of the Johns Hopkins Hospital since 1928.

It comprises records of the 158[3] patients admitted to the clinic between November 1, 1928 and November 1, 1933, all of whom at

[1] Aided by grants from the Commonwealth Fund, the Milbank Memorial Fund and the Maryland Tuberculosis Association.

[2] Grateful acknowledgment is made of the assistance of Dr. W. H. Frost, Professor of Epidemiology, who directed the compilation and analysis of data from clinical records.

[3] The 158 children of this study form part of a group of 170 whose records have been subject of an earlier paper by the author entitled "Mortality in Tuberculin-positive Infants," *Bulletin of the Johns Hopkins Hospital*, 1936, *59:* 1. Twelve records could not be used in the present study: four because calcification was already present when infection was discovered and 8 others because of insufficient X-ray observations.

the time of entry into this study were (1) under 2 years of age, (2) tuberculin positive[4] and (3) showing, on X-ray, no evidence of calcification, and (4) have since been followed with serial X-rays for periods ranging from less than 1 to more than 5 years. Except for these conditions the series is unselected; that is, it includes all the children admitted between the specified dates who fulfilled these requirements.

Of the 158 children accepted for this study, 65 were white and 93 were colored. The age at which the Mantoux test was found positive varied from 1 to 23 months, the average being 13 months. The onset of infection cannot be more exactly dated because, with few exceptions, the infants were not known to the clinic before they had become tuberculin-positive.

The frequency of X-ray examinations varied, being determined by such factors as the severity of the child's infection and the cooperation of the family. For the group as a whole, the average number of chest plates taken during the first year subsequent to the discovery of infection was 4.5; during the second year, 2.2; during the third year, 1.7; during the fourth year, 1.4; during the fifth year, 1.2. Single postero-anterior X-rays taken at a standard distance were the usual routine, oblique and lateral views being taken only exceptionally. Stereoscopic views were not used. The usual technical difficulties in taking good chest plates of infants were encountered, a re-examination by X-ray often being necessary.

Prior to 1933 the films, as taken, were read by various observers; but since 1933 all have been read by the author, who also has made a final review of the whole series of films in every case. In this review, the effort was made to interpret each film, so far as possible, independently, and the rule followed was to accept as evidence of calcification only unmistakable refractile, irregular shadows. However, in the longer series, in which the earlier films were technically inferior, it is probable that the identification of calcium was in some degree influenced by the knowledge that it was confirmed by the later films; and that in some instances calcification is identified with more confidence and recognized a little earlier than it would have been without the confirmatory evidence.

The exact time-interval after the discovery of infection at which intrathoracic calcification was first noted was recorded in all cases, and as in each patient at least

[4] From 1928 to 1934 the Mantoux test was carried out with Old Tuberculin furnished by the Bureau of Animal Industry. Since 1934 all tests have been made with Old Tuberculin standardized by Aronson and purchased from the Gilliland Laboratories. Control tests with broth have been used routinely. Children found to be negative to the initial test dose of 0.01 mgm. or 0.1 mgm. are retested with 1.0 mgm.

one X-ray was taken and usually more within each 12-month period dating from the first film, the data show, with fair accuracy, the proportion of patients who developed recognizable calcification within each successive year from the beginning of observation.[5]

COMPILATION OF DATA

On November 1, 1934, when these records were compiled, all the children in the series had been observed in the clinic for at least one year, and diminishing proportions for longer periods up to six years. Therefore, in calculating the proportions of children developing calcification in each successive year, it is necessary to take account, year by year, of the changing numbers "at risk," that is, remaining under observation and not already showing calcification. The successive steps in the procedure are shown in Table I, which may be described as follows.

The study starts (col. 1) with 158 children, alive, under observation, and showing initially no deposition of calcium. Of these 158 patients, 31 were observed less than one year, and when last examined showed no evidence of calcification. This number includes 24 (col. 2) who died, and 7 (col. 3) who were "withdrawn" in the sense that their *last* recorded X-ray was at an interval of less than 12 months from their initial examination. Counting these 31 "withdrawals," living and dead, as having been under observation for an average of one-half year, the mean number under effective observation throughout the year was $158 - 1/2(24 + 7) = 142.5$, as shown in column 4. Within this year the first evidence of intrathoracic calcification was observed in 24 children (col. 5), which is 16.8 per cent (col. 6) of the mean number "at risk" (col. 4).

At the beginning of the next year there remained under observation, living and without observed evidence of calcification, 103 children (col. 1), this number being the original 158 minus those withdrawn (living and dead) and those having shown evidence of calcification

[5] Where a full 12-month period passed without an X-ray, the case has been included in the tabulation provided the next X-ray was negative, but excluded if it showed calcification which could not be dated. The number of cases in which observation was thus interrupted is so small that their statistical treatment does not appreciably influence the result.

within the first year. From this point the calculation proceeds year by year in the same way as above. Thus, as shown in column 6, evidence of calcification developed during the first year in 16.8 per cent of the children under effective observation: during the second year calcification was shown in 36.7 per cent of the remainder; during the third year in 28.6 per cent of the remainder, and so on to the end of the fourth year.

The figures in column 6 may be used to calculate the proportion of the original number who may reasonably be expected to show evidence of calcification by the *end* of 1, 2, . . . 5 years, as follows. Since

TABLE I

Development of intrathoracic calcification in 158 patients infected with tuberculosis before two years of age

INTERVAL IN YEARS FROM FIRST X-RAY OBSERVATION	(1) NUMBER WITHOUT OBSERVED CALCIFICATION AT BEGINNING OF INTERVAL	(2) NUMBER WITHDRAWN FROM OBSERVATION DURING INTERVAL, WITHOUT OBSERVED CALCIFICATION: By death	(3) NUMBER WITHDRAWN FROM OBSERVATION DURING INTERVAL, WITHOUT OBSERVED CALCIFICATION: By end of observation (living)	(4) MEAN NUMBER UNDER OBSERVATION DURING INTERVAL = (1) − 1/2 [(2) + (3)]	(5) SHOWING FIRST EVIDENCE OF CALCIFICATION DURING INTERVAL: Number	(6) SHOWING FIRST EVIDENCE OF CALCIFICATION DURING INTERVAL: Per cent of (4)	(7) PERCENTAGE SHOWING CALCIFICATION UP TO END OF EACH INTERVAL
1	158	24	7	142.5	24	16.8	16.8
2	103	2	24	90.0	33	36.7	47.3
3	44	0	11	38.5	11	28.6	62.4
4	22	0	4	20.0	2	10.0	66.1
5	16	0	9	11.5	0		66.1

16.8 per cent of those "at risk" show calcification within the first year, the proportion remaining without calcification at the beginning of the second year is 100 − 16.8 = 83.2 per cent. Those showing their first evidence of calcification within the second year (see col. 6) are 36.7 per cent of this *remainder*, which is equivalent to .832 × 36.7 per cent = 30.5 per cent of the *original* number. Then, the proportion of the original number showing first evidence of calcification is 16.8 per cent in the first year and 30.5 per cent in the second year, and in the first two years is 16.8 + 30.5 = 47.3 per cent, as shown in column 7, which gives corresponding figures for 3, 4 and 5 years.

PROPORTIONS SHOWING CALCIFICATION AT VARIOUS INTERVALS

Utilizing the figures in column 7 of Table I, and summarizing a similar detailed tabulation for each of the two races, Table II shows in condensed form the rate of development of the first recorded intrathoracic calcification for the 65 white patients, the 93 colored patients, and for the two races combined. It can be seen at a glance that the two races are much alike in the proportion of cases under observation which at any time-period show evidence of intrathoracic calcification.

When the two races are combined, patients surviving the discovery of their infection one full year are found to have developed calcification in 17 per cent of the cases. This proportion had risen to 47

TABLE II

Development of intrathoracic calcification in 65 white and 93 colored patients infected with tuberculosis before two years of age

INTERVAL IN YEARS FROM FIRST X-RAY OBSERVATION	PERCENTAGE SHOWING CALCIFICATION UP TO END OF EACH INTERVAL		
	White	Colored	White and colored
1	14.9	18.3	16.8
2	52.2	43.3	47.3
3	58.8	64.6	62.4
4	63.4	67.8	66.1
5	63.4	67.8	66.1

per cent by the end of the second year of observation, to 62 per cent by the end of the third year, and to 66 per cent by the end of the fourth year, after which no further calcifications occurred in the small group who continued under observation through the fifth year. In children of this series, infected in infancy and surviving their infection four years, calcification had made its appearance in two-thirds of the patients.

Observations on the children whose records form the basis for this paper began during infancy when Vitamin D is usually prescribed as an addition to the diet. They received routinely 3 teasponfuls of cod liver oil daily and unless they were above normal weight standards, they continued to take cod liver oil after the period of infancy was past. Although there were recorded many temporary lapses

from its use, it is possible that its more or less continuous use may have influenced favorably the deposition of calcium.

The youngest patient in our series in whom intrathoracic calcification was observed was ten months old. This infant was colored and had been exposed for the first month of life. A positive tuberculin reaction was demonstrated at six weeks of age.

RACIAL DIFFERENCES: CHARACTER OF LESIONS AT TIME FIRST CALCIUM WAS NOTED

One might suppose that negro children, who suffer a mortality from tuberculosis more than twice that noted for white children, would show calcification either less frequently or less early, but in this series the rates for the two races are nearly identical. It is probably important, however, that the races differed widely in the extent of unhealed lesion visible in the X-ray at the time the first intrathoracic calcification was noted. Abnormal shadows noted as evidence of unhealed lesion were grossly enlarged lymph nodes, areas of unresolved tuberculous pneumonia, or both. Such lesions might be located on either side of the chest and were not necessarily at the site of earliest calcification. Children displaying such lesions, even though there is evidence of regression by the time calcification makes its appearance, are presumably in a more precarious state than those whose X-rays show no definite pathological change apart from calcification itself. Among 40 infected colored children who showed evidence of beginning calcification, there were 22, or 55 per cent, in whom unhealed lesion was still discernible; while among 30 white children displaying first calcification there were only 9, or 30 per cent, who had such lesions visible in X-rays. Moreover, in the 30 white patients there followed a benign course for the remaining period of observation once calcification had made its appearance, while during the same length of time two deaths from tuberculosis occurred among the 40 colored patients.[6] In groups so small these differences between the two races in character of lesion and mortality after calcification had made its appearance are no more than sug-

[6] A third death from tuberculosis occurred in the colored group about six months after these records were compiled.

gestive, but they are consistent with many other facts indicative of higher resistance in the white race.

RELATION OF RATE OF CALCIFICATION TO SEVERITY OF LESION

When the 158 patients are classified according to the most extensive lesion observed roentgenologically prior to the appearance of calcification, it is found that those exhibiting parenchymal lesions showed deposits of calcium in a higher proportion of cases than those in whom parenchymal lesion was never noted. These differences in rates of calcification according to the extent of preceding active lesion are shown in Table III and in Figure 1. The patients are divided into three groups on the basis of their most definitive X-ray findings. The first group, with parenchymal lesions, numbered 78; the second, with enlarged tracheobronchial nodes but no noted lung lesion, consisted of 27 patients; the third group contained 53 patients in whom no definite intrathoracic lesion of any kind was noted prior to the first recorded calcification.

The figures are too small for exact quantitative comparisons, but, taking into account their consistency, they show pretty definitely that demonstrable calcification may be expected in more than 80 per cent of children surviving a definite parenchymal lesion, in about two-thirds of those who have shown enlarged nodes without discovered lung lesions, and in not much over one-third of those in whom no lesion had been observed.

It is of particular interest that the diagnosis of lesion of the tracheobronchial nodes was confirmed eventually by the appearance of calcification in a high proportion of cases followed as long as three or four years after nodal enlargement was first recorded.

A second point to be emphasized in Table III is that repeated negative chest plates in early childhood do not rule out thoracic lesion, and the probability that calcification will eventually develop in such cases is roughly one-half that for cases in which well-defined lesions have been observed.

SITES OF INTRATHORACIC CALCIFICATION AS DETERMINED BY X-RAY

Irrespective of location or extent of active lesion, if calcium is deposited, it appears *first* and most frequently in X-rays of the chest

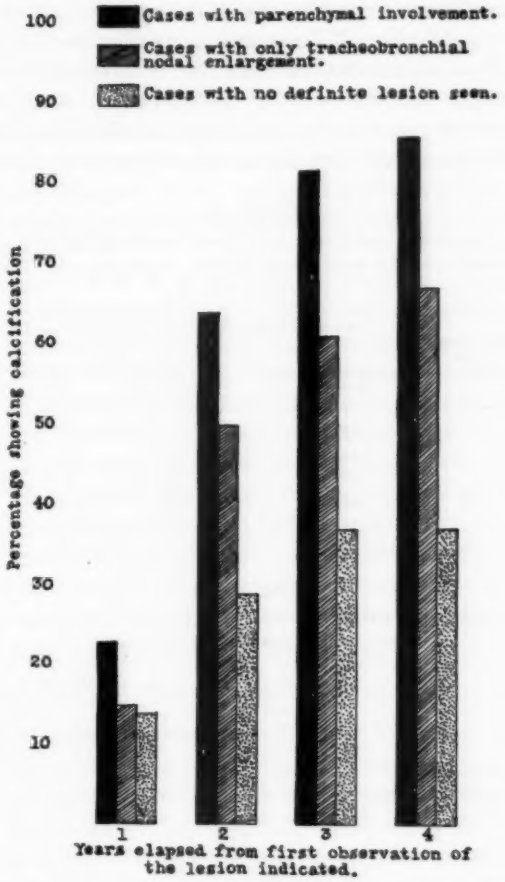

FIG. 1. PERCENTAGE OF CHILDREN SHOWING CALCIFICATION AT END OF FIRST, SECOND, THIRD AND FOURTH YEARS, CLASSIFIED ACCORDING TO CHARACTER OF MOST DEFINITE LESION OBSERVED PREVIOUSLY

in the nodes at the hilum. This is shown in Table IV. In 67 per cent of the 70 cases developing calcification, deposits were first noted at the hilum alone; in less than 9 per cent was the lung parenchyma alone the site of first calcification; and in the remaining 24 per cent,

calcium was observed simultaneously at the hilum and in the lung substance. Combining all instances of calcification at the hilum, the tracheobronchial nodes were the site of first calcification in 91 per cent of the calcified cases of this series. In contrast to this, the lung parenchyma, either alone or together with the hilum, showed the first evidence of calcification in only 33 per cent of the cases.

TABLE III

Development of intrathoracic calcification in 65 white and 93 colored patients in successive yearly intervals after their most definite preceding lesion was noted (illustrated by figure 1)

INTERVAL IN YEARS AFTER FIRST X-RAY TO SHOW INDICATED LESION	PERCENTAGE SHOWING CALCIFICATION UP TO END OF INTERVAL		
	Parenchymal lesions 78 patients	Tracheobronchial nodes only 27 patients	No definite active lesion 53 patients
1	22.7	15.4	14.1
2	64.1	50.1	27.6
3	82.0	60.6	36.6
4	86.0	67.2	36.6
5	86.0	67.2	36.6

TABLE IV

Location of the first recorded intrathoracic calcification in 70 cases, according to whether or not parenchymal lesion had been noted earlier

	NUMBER OF CASES WITH CALCIFICATION	AT HILUM ONLY		IN LUNG FIELD ONLY		BOTH AT HILUM AND IN LUNG	
		Number	Per cent	Number	Per cent	Number	Per cent
Parenchymal lesion earlier.....	41	24	58.5	5	12.2	12	29.3
No parenchymal lesion noted....	29	23	79.3	1	3.4	5	17.2
	70	47	67.1	6	8.6	17	24.3

In Table IV are shown 47 cases displaying first calcification only at the hilum. This group has been studied for the subsequent appearance of calcification in the lung parenchyma. Two cases were discarded because no further X-rays had been taken, but of the remaining 45, 20 per cent were found to have developed parenchymal calcification during the first year, 26 per cent by the end of two years, and 36 per cent by the end of three years of later observation.

When the 70 patients with calcification were studied with reference to the location of calcium deposits and the site of lesions observed earlier, it was found that 14, or one-fifth of the group, had given no definite evidence of a preceding intrathoracic lesion. In the remaining 56 cases, parenchymal or nodal lesions had been recorded; and in 51, or 91 per cent of these, calcium was eventually deposited on the corresponding side of the thorax. In the other 5 cases, 9 per cent, it made its appearance only on the opposite side where no lesion had been seen.

In 41 cases of the 56, a preceding *parenchymal* lesion had been noted, and more than half of these, 56 per cent, eventually developed parenchymal calcification at the expected site. In the remaining 15 cases, where only enlarged tracheobronchial lymph nodes had been noted, calcification developed in the lung parenchyma of the corresponding side in five, or one-third of the cases.

In the present series of cases calcium was noted with greater frequency on the right side of the thorax than on the left. In 41 cases it was observed only on the right; in 16 cases only on the left; and in 13 instances it was bilateral. Thus the right side was involved in $41 + 13 = 54$ cases, or 77 per cent, and the left side in $16 + 13 = 29$ cases, or 41 per cent. This is in accordance with the usual experience that lesions of the right thorax are observed more frequently.

ALTERATIONS IN X-RAY APPEARANCE OF CALCIFICATION

It becomes apparent from a study of serial X-rays of cases developing calcification that the size, shape, refractility, and location of the calcified mass tend to alter with the passage of time. When first seen, the deposits of calcium usually present a granular appearance, the granules being often not very closely packed. During the next few months new granules appear, refractility tends to increase, and the contraction of the healing lesion usually draws the granules of calcium more closely together, gradually making them into a more or less compact mass, but one which at this stage has characteristically irregular margins. This is the period when small deposits of calcium present their most definite and characteristic appearance. As calcium grows older, say three or four years after its deposition has begun, the irregularity and refractility tend to be less marked.

The edges of the mass become rounded rather than sharp, the shadow is less bright in appearance; and under such conditions, with no knowledge of earlier X-ray findings, it is sometimes difficult to distinguish calcification at the hilum from blood vessels seen in cross-section.

Also, as the child's lung grows, and as the tuberculous lesion contracts in the process of healing, deposits of calcium either in the lymph nodes at the hilum or in the lung parenchyma tend to occupy a more central position in the chest. Depending upon the size of the calcified mass and upon its original position, it may or may not remain permanently visible in the ordinary postero-anterior view. It is a fairly common experience that tracheobronchial lymph nodes, in which unmistakable calcification was noted earlier, disappear behind the sternum, so that postero-anterior views of the chest may disclose no evidence of tuberculosis. The increased markings at the hilum characteristic of the normal chest, as infancy is left behind, may in themselves be enough to obscure evidences of calcification unless the masses of calcium are large. In 5 of our 70 cases small deposits of calcium, which are quite definitely shown in several X-rays taken three or four years ago, are not visible in films taken more recently.

ABSORPTION OF CALCIFICATION

There is evidence that in the occasional case calcium can be completely absorbed leaving no trace behind it. For inquiry into this possibility one must study calcium in an exposed position, such as the peripheral lung-field, where it cannot be obscured by mediastinal structures. The mass must be large enough to preclude the possibility of being covered by a rib.

Such a case is T-128 of the present series, a white male, who developed a calcified pulmonary nodule in the right upper lobe at the level of the fourth interspace, counted posteriorly. The nodule was first recorded in September, 1930, when the patient was 26 months old. It increased in refractility and in number of granules, becoming a fairly compact mass by October, 1931, when it measured 10 x 7 mm. A year later in October, 1932, it was appreciably smaller, measuring 4 x 4 mm. In November, 1933, it was only 2 x 2 mm.

and was distinctly less refractile. In November, 1934, four years after its first appearance, no trace of the nodule could be found and repeated X-rays since that date have failed to disclose it. Calcification of the right tracheobronchial lymph nodes, first recorded in October, 1931, is still evident, although a lateral view is necessary to give an adequate idea of the extent of calcification.

It is apparent from such observations that changes in the location, size, shape and refractile quality of deposits of calcium may occur with time, making small deposits less and less easy to identify. It is thus quite possible for a patient in whom an unmistakable calcified lesion has been demonstrable during childhood to arrive at adult life with no roentgenological stigmata of his earlier tuberculous lesion.

ALLERGY IN CHILDREN EXHIBITING CALCIFICATION

Within the past few months 46 patients from the group of 70 who had displayed calcification more than 2 years previously have been retested with 0.01 mg. of Old Tuberculin. The average length of time from the first recorded calcification to the recent tuberculin test was 4 years and 3 months. Of the 46 tested, 41 reacted positively to 0.01 mgm. and 5 failed to react, but 4 of these who have been tested with 0.1 mgm. showed definite reactions. The fifth child has had no further tests applied. In this small series, tested more than 2 years after intrathoracic calcification was first noted, no certain instances of loss of allergy have been noted.

With reference to the possible rôle of continuing intrafamilial exposure in maintaining allergy in the retested children, it is of interest that in 11 of the 46 prolonged search had failed to reveal household association at any time with an infective case; in 31 definite exposure occurring in infancy had been terminated for periods ranging from a minimum of eighteen months up to more than 8 years prior to the last recorded retest. In only 4 of the 46 children was there known exposure at the time of retesting; and it was one of these four who failed to react to 0.01 mgm. of tuberculin, and as yet has not been tested with an increased amount.

A patient not belonging to this series but followed in the clinic from five months of age is of interest because of low allergy exhibited and its early loss. This child, T-103, was a colored female admitted

for observation because of supposed household exposure to tuberculosis, which on investigation was not confirmed. After several negative tests, she gave a doubtful reaction to 1.0 mgm. of tuberculin at 18 months of age, but at that time gave no evidence of lesion on X-ray examination. At 23 months of age a bulging left bronchial node was visible, but the child did not react to 0.1 mgm., the only test applied. More than a year later she was shown to be definitely positive to 1.0 mgm., the node meanwhile remaining enlarged. At 4 years and 7 months calcification at the site of lesion was first noted and was observed to increase during the next twelve months, when at the age of 5 years and 7 months tuberculin failed to elicit a reaction until a test dose of 10 mgm. was used. Nearly two years after the first observed calcium, at 6 years and 4 months of age, she was still negative to a 5 mgm. test.

The demonstration of calcified tuberculous lesions in children of school age who react negatively to 1.0 mgm. of tuberculin is not especially unusual. This case, however, is considered to be of special interest because of the fact that allergy was so low even during the acute stage of lesion and so soon fell below the level of the usual maximum test dose of 1.0 mgm. of tuberculin.

SUMMARY

1. A series of 158 children, of whom 65 were white and 93 colored, found to be infected with tuberculosis before reaching two years of age, have been kept under observation by X-ray for periods ranging from a few months to more than five years. They afford material for a study of intrathoracic calcification.

2. It was found that calcification appeared in the chest in about 17 per cent of children observed one year after the discovery of tuberculous infection. This proportion rose to 47 per cent by the end of two years of observation; to 62 per cent by the end of three years; and to 66 per cent by the end of four years.

3. White and colored children developed calcification at equal rates, but the colored had unhealed lesions associated with first calcification in 55 per cent of the cases, the white in 30 per cent.

4. The proportion of cases developing calcification varied with the extent of lesion. Within a four-year period, it was observed in 86

per cent of children who had shown parenchymal lesion, in 67 per cent of those who had shown definite tracheobronchial node involvement without parenchymal lesion, and in 36 per cent of those in whom no definite lesion had ever been recorded.

5. In 90 per cent of the cases calcification appeared first in the tracheobronchial lymph nodes. Associated calcifying pulmonary nodules were observed simultaneously in about one-third of these cases, and in another third pulmonary nodules appeared later.

6. About one-fifth of the cases which developed calcification had shown no definite lesion in earlier X-rays. In the remaining four-fifths, calcification usually took place on the side of the thorax where the active lesion had been noted, but in 9 per cent it appeared only on the opposite side where no lesion had been seen.

7. Serial X-rays demonstrate that small deposits of calcium may become indistinguishable with time, due to changes in the calcified mass, or to its becoming hidden by mediastinal structures. An instance is cited of the absorption and disappearance of a calcified parenchymal nodule within four years of its first appearance.

8. Forty-six cases of this series of patients in whom calcification had been noted more than 2 years previously have been tested recently with Old Tuberculin. With the possible exception of one case failing to react to 0.01 mgm. and not retested, no instance of loss of allergy has been found. However, in a case which is not included in the present series, allergy was shown to be greatly diminished as early as one year after intrathoracic calcification was first recorded.

PROTECTIVE ACTION OF SULFANILAMIDE AND ANTI-MENINGOCOCCUS SERUM ON MENINGOCOCCUS INFECTION OF MICE

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In 1933 Miller (1) observed that meningococci, when suspended in hog's gastric mucin, were highly virulent for mice following intraperitoneal injection. Nungester, Wolf and Jourdonais (2), in 1932, reported the use of mucin to enhance the virulence of certain other organisms. Murray (3), in his monograph on the meningococcus, which was written before the use of mucin, emphasized the difficulty in interpretation and the variability of results in experimental meningococcus infection in the usual laboratory animal. The methods described by Miller (1) and by Miller and Castles (4) have made it possible to study experimental meningococcus infections under conditions which insure a uniformly high degree of virulence. Although the natural immunity of mice for meningococci is lost when the organisms are injected intraperitoneally in a mucin suspension, specific protection by antimeningococcus sera may be accomplished. It is therefore possible to judge the comparative protective action of the several known therapeutic agents in mice infected experimentally with meningococci.

Buttle, Gray and Stephenson (5) first observed the protective action of sulfanilamide in mice infected with meningococci. Proom (6) verified and extended these original observations. Schwentker, Gelman and Long (7) recently reported favorable results in the treatment of ten patients with meningococcus meningitis.

It is the purpose of the present paper to report the titrated protective action of sulfanilamide in meningococcus infection of mice and to compare this with the protective action of antimeningococcus

serum.[1] In addition to the effect of the two therapeutic agents when employed separately, the degree of protection afforded by a combination of sulfanilamide and antimeningococcus serum has been studied and will also be reported.

METHOD

Two virulent strains of meningococci recently isolated from the spinal fluid of patients suffering from meningococcus meningitis were employed. The strains were both of the Group I–III. No attempt was made to increase their virulence after isolation from the patients by repeated transfer through mice. The organisms were maintained on artificial media for about four weeks before they were used for the purposes of the experiment.

Eight-hour cultures grown aërobically on rabbit-blood agar slants were used for the mouse inoculations, the organisms having been subcultured twice during the preceding 24 hours. The inoculated surface area of the blood-agar slants as well as the size of the inoculum were kept relatively constant. The abundant 8-hour growth of the meningococci on the blood-agar slant was resuspended in plain infusion broth, pH 7.6; in the case of strain Ball (Table I) 1.2 cc. of broth was used with strain Oakley (Table II) 2.0 cc. of broth. The difference in the amount of broth used was ascertained by finding the quantity of diluent necessary to adjust the minimal lethal dose to 10^{-8} cc. of the original broth suspension. Tenfold dilutions of the original broth suspension were made in mucin. The mice were inoculated intraperitoneally with 0.5 cc. of the mucin suspension of organisms. Controls received dilutions of organisms in mucin ranging from 10^{-7} to 10^{-10} cc. of the original broth suspension. In all except about 2 per cent of the control mice, the M.F.D. (minimum fatal dose) of organisms was established at 10^{-8} cc. of the original broth culture. In the remaining 2 per cent it was 10^{-9} cc. The quantity of the infecting dose of organisms was calculated on the basis of the number of M.F.D. received. The mucin suspension of meningococci was injected into the mice within one-half hour after the dilutions in mucin had been made.

The technique described by Miller and Castles (4) was regularly employed with the variation of using 0.5 cc. instead of 1 cc. of the mucin suspension of organisms for the intraperitoneal inoculations. The mucin was obtained from the Wilson Laboratories in Chicago and is designated as Granular Mucin (Hog's Gastric). It was used in 5 per cent suspensions containing 1 per cent glucose and adjusted to pH 7.3.

Administration of sulfanilamide: An 0.8 per cent solution of sulfanilamide was

[1] Antimeningococcus serum was kindly supplied by Dr. Wadsworth and Dr. Kirkbride from the Laboratories of the New York State Board of Health, Albany, New York. The use of this type of antimeningococcus serum in the treatment of patients has been previously reported (8).

prepared by dissolving the drug in a physiological solution of sodium chloride. The saline solution was heated to the boiling point, removed from the flame and the drug then added. This method of preparation was similar to that of Long and Bliss (9) in the treatment of mice infected with streptococci. When not being used, the sulfanilamide solution was kept at room temperature and it was not used any later than four days after the time of preparation. The mice were treated with amounts of the drug ranging from 8 mgm. to 0.08 mgm. as indicated in Tables I and II. Proper dilutions of the original 0.8 per cent solution were made so that the volume of solution injected was kept at 1.0 cc. in every instance. The sulfanilamide solution was injected subcutaneously immediately after the injection of organisms.

Administration of serum: New York State concentrated antimeningococcus serum (nos. 28 and 29) was used exclusively. Dilutions of serum were made in physiological saline solution, so that 0.5 cc. contained amounts of serum varying from 0.1 cc. to 0.001 cc. (Table II). The serum solution was injected intraperitoneally, and as in the case of sulfanilamide the serum was injected immediately after the inoculation with meningococci.

Blood cultures from the tail were taken at various time intervals following the inoculation with meningococci. A drop of blood was streaked on the surface of a blood-agar plate. The average findings of the 8-hour blood cultures are recorded in the tables.

Swiss mice were used in all of the experiments. Treated mice that did not succumb to the infection were kept for one week to assure ultimate survival.

EXPERIMENTAL

Protective action of sulfanilamide: The effect of sulfanilamide in titrated amounts on the degree of recovery of mice infected with various M.F.D. of meningococci (strain Ball) in mucin suspension has been recorded in Table I.

From the Table it may be seen that when the maximum dose of sulfanilamide (8 mgm.) was used, the upper limit of complete protection was found in the group of mice receiving 100,000 M.F.D. of meningococci in mucin. With a larger inoculum of organisms the same quantity of sulfanilamide afforded little or no protection. When 4 mgms. of sulfanilamide were used, complete protection against 10,000 M.F.D. occurred. 0.8 mgm. of sulfanilamide promoted recovery of two mice in a group of 6 inoculated with 10,000 M.F.D. 0.08 mgm. of sulfanilamide gave no protection to the mice receiving 10,000 M.F.D. of organisms. Blood cultures taken 8 hours after the mice were infected were found to be negative in the groups of

mice in which complete recovery occurred, regardless of the dosage of organisms or drug.

COMPARISON OF THE PROTECTIVE ACTION OF SULFANILAMIDE AND ANTIMENINGOCOCCUS SERUM (NEW YORK STATE)

Table II contains the results of protection tests done with sulfanilamide alone, serum alone, and the two materials in combination. With respect to the data which deal with a comparison of the effectiveness of sulfanilamide in relation to serum, it may be noted from the Table that 8 mgm. of sulfanilamide (the maximum quantity used)

TABLE I

Titrated protective action of sulfanilamide

(Strain Ball)

SULFANILAMIDE	10 M*		1 M		100 T		10 T		1 T		BLOOD CULTURES—AVERAGE FINDINGS 8 HOURS AFTER INJECTION OF MENINGOCOCCI				
	D†	S	D	S	D	S	D	S	D	S	10 M	1 M	100 T	10 T	1 T
mgm.															
8	6	0	5	1	0	6					+++	++	−		
4			6	0	2	4	0	6				+++	+	−	
1.6					5	1	2	4	0	2			++	+	+
0.8					6	0	4	2	0	2			+++	+++	+++
0.08							6	0	5	1				+++	+++

Controls—30 mice died following injection of 10^{-8} cc. of meningococci (see Method).

* 10 M—10,000,000 M.F.D. (Minimum Fatal Doses) Meningococci. 100 T—100,000 M.F.D. (Minimum Fatal Doses) Meningococci.

† D—Died. S—Survived.

gave no protection against 10,000,000 lethal doses, protected 3 out of 6 mice receiving 1,000,000 lethal doses, and afforded 100 per cent protection for 6 mice receiving 100,000 M.F.D. By comparison, 0.1 cc. antimeningococcus serum (the maximum quantity employed) afforded only 50 per cent protection in 6 mice receiving 100,000 M.F.D. Although these findings do not establish the relative values of the therapeutic agents, they serve as a basis for estimating the curative effect of a selected dosage of the drug in relation to 0.1 cc. of serum. The additional results in the Table indicate that when the dosage of sulfanilamide is reduced by one-half (4 mgm.) the protective value is equal to or slightly greater than that afforded

by a tenfold dilution of serum. It is obvious that if 8 mgm. of sulfanilamide were diluted 10 times, as in the case of the serum, then the effect of the drug would not be equal to that of serum.

It is important to note for purposes of comparison later, that neither 1.6 mgm. of sulfanilamide nor 0.001 cc. of antimeningococcus serum, when used separately to treat mice infected with 100,000 M.F.D., gave any degree of protection against this second strain of meningococcus.

TABLE II

Comparative protective action of sulfanilamide and antimeningococcus serum

(Strain Oakley)

SULFANILAMIDE	SERUM	10 M		1 M		100 T		10 T		BLOOD CULTURES—AVERAGE FINDINGS 8 HOURS AFTER INJECTION OF MENINGOCOCCI			
		D	S	D	S	D	S	D	S	10 M	1 M	100 T	10 T
mgm.	cc.												
8		6	0	3	3	0	6			+++	+	−	
4		4	0	4	2	3	3			+++	+	−	
1.6						9	0					+	
	0.1	6	0	5	1	3	3			+++	+	+	
	0.01			6	0	4	2	0	6		+	+	−
	0.005			4	0	4	2	0	3		++	+	−
	0.001					9	0	1	2			+++	−
8	0.1	3	3	0	6					−	−		
4	0.01	5	1	0	6					+	−		
4	0.005	5	1	2	4	0	6			+	−	−	
1.6	0.001					0	9					−	

Controls—40 mice died following injection of 10^{-8} cc. of meningococci (see Method). See legends—Table I.

COMBINATION OF SULFANILAMIDE AND ANTIMENINGOCOCCUS SERUM

The combined action of sulfanilamide and antimeningococcus serum gave a higher degree of protection than did either sulfanilamide or serum alone. This point is illustrated in Table II where it may be noted that fifty per cent protection was found in the case of mice infected with 10,000,000 M.F.D. of meningococci, and treated with a combination of 8 mgm. of sulfanilamide and 0.1 cc. of serum. Individually, with the same dosage of sulfanilamide or serum and the

same lethal level of infecting organisms, none of the mice survived. The treatment of mice receiving 100,000 M.F.D. of organisms with a combination of 1.6 mgm. of sulfanilamide and 0.001 cc. of serum resulted in complete recovery. When, in comparable experiments, the same quantity of the therapeutic agents was used individually rather than in the combined state, none of the mice so treated survived. Other instances of improved protective action by the use of sulfanilamide and serum in combination may be noted in Table II.

The incidence of negative blood cultures at 8 hours after the time of infection was greater in the series of mice treated with a combination of sulfanilamide and serum than with the two therapeutic agents used separately.

The average time of survival of the control mice, 98 per cent of which died after the injection of 10^{-8} cc. of the original broth suspension in mucin, and 2 per cent with 10^{-9} cc., was 24 hours. Cultures from the heart blood of these mice taken soon after death were uniformly positive for meningococci. Two treated mice, not included in the series, died 3 hours after the injection of the therapeutic agent, but autopsy findings revealed evidence of injury due to the injection. The survival time of the treated mice that died was proportional to the number of M.F.D. of meningococci injected and the amount of the therapeutic agent received. It varied between 12 and 36 hours. None of the mice living longer than 36 hours failed to survive.

In a small group of mice, antipneumococcus serum was used to replace antimeningococcus serum in the combination with sulfanilamide. Four mice infected with 100,000 M.F.D. of meningococci (strain Oakley) received 1.6 mgm. of sulfanilamide and 0.01 cc. of antipneumococcus serum.[2] None of these mice survived. It has been previously shown that none of the 9 mice which received the same infecting level of meningococci (100,000 M.F.D.) and were treated with 1.6 mgm. of sulfanilamide survived, whereas complete protection was afforded to the 9 mice receiving a combination of 1.6 mgm. of sulfanilamide and 0.001 cc. of antimeningococcus serum. This fact would suggest that enhanced protective activity obtained

[2] Antipneumococcus serum—Type I—Concentrated (Lederle).

by the combination of sulfanilamide and antimeningococcus serum is dependent upon the presence of antibodies in the serum which are specific for the particular type of infecting organism used.

While this paper was being prepared, Rosenthal, Bauer and Branham (10) reported the therapeutic action of di-sulfanilamide as well as sulfanilamide upon meningococcus infections in mice. They found a marked curative action with both drugs, the former having a slightly more pronounced effect than the latter. Branham (11) also reported the results of the combined action of sulfanilamide and antimeningococcus serum. Her conclusions were that the combination of serum and drug therapy yielded much better results than either alone. The results of the present report are in agreement with those of Branham (11).

DISCUSSION

It may be concluded from the foregoing experiments that a single subcutaneous injection of sulfanilamide exerts a marked protective influence on mice infected experimentally by intraperitoneal injections of meningococci suspended in mucin. These observations confirm those of Proom (6) who noted that, unlike experimental streptococcal infection in mice where it is necessary to administer repeated doses of sulfanilamide in order to promote recovery, in the mice infected with meningococci, a single dose of sulfanilamide given immediately after the injection of organisms may suffice. 0.1 cc. of antimeningococcus serum when compared with 8 mgm. of sulfanilamide gave a slightly lower degree of protection.

The combination of sulfanilamide and antimeningococcus serum resulted in a greater protective influence than that of either the sulfanilamide or serum alone. A point was reached in the dilution of sulfanilamide and of serum where neither of these therapeutic agents used individually gave any degree of protection. However, when combined, their protective influence now became complete. The combination of sulfanilamide and serum also tended to sterilize the blood stream of the infected mice much more rapidly than did either one or the other of these agents by itself.

It would be of interest to determine the clinical value of the combined action of sulfanilamide and antimeningococcus serum in the treatment of patients suffering from meningococcus meningitis.

CONCLUSIONS

1. The protective influence of 8 mgm. of sulfanilamide is comparable to that of 0.1 cc. of a highly potent grade of antimeningococcus serum.

2. The combination of sulfanilamide and antimeningococcus serum produces a greater degree of protection than either one of the agents by itself. In the treatment of a few animals, the use of antipneumococcus serum instead of antimeningococcus serum in the combined therapy failed to give enhanced protection.

3. The percentage of positive blood cultures, taken 8 hours after the mice were infected, was lower in the group of mice treated with the combination of sulfanilamide and antimeningococcus serum than in the groups treated with these therapeutic agents individually.

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A PECULIAR CASE OF ENCEPHALITIS AND MYOSITIS

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The report of the following case is made because a search of the literature of the past twenty years fails to reveal any description of a muscle lesion closely resembling the one herein described. Not only does this particular muscle lesion appear to be unique, but its association with a very fulminating encephalitis, thereby causing confusion in the interpretation of the clinical picture, makes it particularly worthy of note.

The only case even remotely resembling this one was just reported by Sättele.[1] His patient was a fifteen year old girl, who, clinically, showed the typical symptoms and signs of progressive muscular dystrophy. Death was caused by respiratory paralysis. Microscopic sections of the earliest lesions showed atrophic muscles with only a slight interfibrillar round cell infiltration. More severely affected muscles showed foci of necrosis associated with greater accumulations of small lymphocytes. In the areas of greatest injury, zones of muscle fibers had been replaced by dense lymphoid cell infiltration.

Unfortunately, the data available from the clinical history of the present case are meagre and inaccurate. The history was difficult to obtain because the patient on examination was almost totally deaf; his voice was blurred and so inaudible as to be barely understandable; and his muddled mental condition detracted still further from the potential reliability of his story. Nor could any additional information be obtained from family or friends.

CASE REPORT

J. H. M. (Unit No. 66980), a white man, 57 years of age. Admitted to the Neuro-surgical Service of the Johns Hopkins Hospital, January 1, 1936.

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[1] Sättele: *Deutsches Arch. f. klin. Med.*, 1937, Bd. 180, S. 202.

Complaint: Weakness in the legs.

Family history: Not obtained.

Past history: Essentially unimportant. There was no knowledge of venereal disease. He had been married for 33 years.

Present illness: Ten years ago, he became very hard of hearing. At the same time he noticed marked weakness of the right thigh muscles. He could walk only by pulling himself about while holding on to objects. Four years ago he could walk with the aid of a cane; 3 years ago crutches became necessary. Deafness has been progressive. There has been associated tinnitus for two years. There has never been any vertigo. Poor vision has been noted for three years; diplopia for one year.

One month ago the patient had a "bad spell," the nature of which could not be determined. Since then has had speech difficulty as well as the continuation and accentuation of his other complaints.

Physical examination: (Only the pertinent points are given.) T. 99.4°; P. 82; R. 20. The patient is an obese white man lying in bed in obvious respiratory distress. Slight cyanosis is present when he is sitting, and is increased when he is lying down. His chest reveals moderate emphysema and râles at both bases. His heart examination is negative. His abdomen is rotund and relaxed. There are external haemorrhoids.

Neurological examination: Cranial nerves: I—Unable to recognize, but differentiates odors fairly well; II—Normal; III, IV and VI—Pupils small and react very little to light; extra-ocular movements normal; no nystagmus; V and VII—No facial anaesthesia or weakness; color reflexes normal; VIII—Bilateral deafness; bone conduction better than air conduction; IX—uvula contracts well in midline; gag reflex is active; X—Phonates so poorly as to be inarticulate; XI—There is no weakness of the sternomastoids or trapezius muscles; XII—No tongue abnormality.

Motor: There is generalized weakness, more marked in the legs, without atrophy. Muscle tone is poor; the hand grips are weak; the legs are rather flaccid.

Sensory: Normal.

Reflexes: The tendon reflexes in the legs are inactive but equal; they are normal in the arms. There are no other abnormal reflexes.

Cerebellum: No abnormalities.

Cerebrum: The patient is disoriented, irrational, euphoric and shows memory loss and personality change.

Laboratory findings: Wassermann—Negative; Haemoglobin—95%; White blood cells—6100 cells. Spinal tap—Fluid clear and colorless; Pressure—normal; Normal response to compression of both jugular veins; Cells—None; Pandy 0; Wassermann 0.

Clinical impression: Presenile cerebral atrophy.

On January 4th, a spinal air injection was performed. The following report of the X-ray taken was made: No gross evidence of abnormality in the ventricular system; considerable cortical atrophy over the right hemisphere. Following the

operation, the patient responded poorly. He was cyanotic, had an unproductive cough and his respirations were labored. His temperature rose rapidly to 105.8°; respirations rose from 18 to 40. On the next day, his respirations became still more labored, and although no definite signs of pneumonia were heard, he was put in an oxygen tent. The next day, January 6th, signs of consolidation were heard over the left base. His condition gradually became worse; T. 106.0°, P. 190, R. 60, and he died at 1 p.m.

The final clinical impression was—Cerebral atrophy. Death following spinal air injection. Lobular pneumonia, left base.

Autopsy (No. 14589) was performed two hours after death. The final anatomical diagnosis follows: Widespread encephalitis; atrophy of the cerebral convolutions; air in the meninges. Intense mononuclear cell infiltration of rectus abdominis and psoas muscles replacing necrotic fibres. Lobular pneumonia, left lower lobe. Hyperplasia of femur marrow. Acute splenic tumor. Emphysema. Encapsulated caseous and calcified tubercle, in right middle lobe. Bilateral pleural adhesions. Early sclerosis of the coronary arteries. Adenoma of thyroid. Chronic urethritis, cystitis, pyelitis and pyelonephritis. Diphtheritic proctitis. Calcified myoma and haemangioma of stomach.

The following significant findings are noted in the autopsy protocol:

External appearance: The body is that of an exceedingly obese elderly white man. The abdomen is protuberant and the musculature flabby.

Abdominal wall, muscles, and abdominal cavity: The abdominal wall is greatly thickened by heavy deposits of adipose tissue. Grapelike masses of fat hang from it into the peritoneal cavity. Numerous sections of rectus abdominis and psoas muscles show gray masses of tissue interrupting the red muscle bundles. No similar change is noted in the diaphragm or other muscles. The omentum and mesentery are bulging with fat.

Heart: The heart weighs 400 grams. It seems large only because of an increased amount of epicardial fat. The coronary arteries show diffuse areas of sclerosis. There are no myocardial or valvular lesions. The aorta is normal except for a few tiny fatty streaks in the posterior aspect of its thoracic portion.

Lungs: There are old pleural adhesions over the left upper lobe. The lungs are somewhat emphysematous. There are patches of red consolidation in the left lower lobe. Its bronchi are filled with exudate. Larger bronchi at the hilum are reddened and filled with gray exudate. There is a calcified and caseous encapsulated tuberculous focus in the right middle lobe.

Spleen: The spleen is enlarged, weighing 410 grams. Its consistence is rather soft; its color is deep red. There are visible gray trabeculae and Malpighian bodies.

Stomach and Intestine: Several small purplish nodules are found in the mucosa of the stomach and jejunum. Hanging externally from the stomach wall at one point of the fundus is a small, densely hard, nodule. The lining of the stomach is rough and nodular without its usual parallel folds. At several points there are

shallow areas of ulceration in the mucosa. In the rectum are several flat yellow areas of diphtheritic exudate covering small red granular areas of ulceration.

Liver: Weighs 1800 grams, and shows no abnormality aside from this increase in size.

Kidneys: They look alike and are of normal size, each weighing 125 grams. Their surfaces are rough and show irregularly scattered coarse scars. The cortex of each is regular. There are a few pelvic haemorrhages.

Thyroid: A small nodule, firm and gray, is found in the right lobe. No external abnormalities are noted in the other viscera, with the exception of the brain.

Brain: The brain is very small. On its removal from the cranial cavity, clear fluid and bubbles of air are noted in the meshes of the pia arachnoid covering its widened sulci. The dural sinuses are normal. There is extreme diffuse atrophy of the cortical convolutions. The blood vessels at the base of the brain show only slight sclerosis.

On sectioning the brain after hardening, the atrophy of the cortex and the separation of the convolutions are even more prominent than on the surface. The ventricles are widened because of the atrophy. There are a few cystic dilatations of the choroid plexus. The cortical atrophy seems most prominent about the left Rolandic fissure. There are numerous tiny patchy areas, reddish or yellowish-red in color, in the left subcortical white matter; another is seen in the temporal lobe, others further posteriorly in the white matter underlying the Rolandic area. Still another section of the brain shows slightly reddish areas, others pale with little yellowish flecks in the paracentral lobule. None of these is larger than 5 mm. in width. Similar patches are seen in the mesencephalon lateral to the substantia nigra and the red nucleus, and others in the narrow portion of the caudate nucleus near the ventricle. On the right side there is a little yellow focus in the white matter lateral to the peduncle, and also in the temporal lobe. Cutting the brain anteriorly brings into view other patches in the frontal lobes and the centrum ovale. In the frontal lobes, the little patches are not confined to the white matter but are also found in the overlying gray portions. In the parietal region the distribution of the lesions is quite abundant, particularly on the left, and other foci are found in both the right and left occipital lobes. No gross lesions are recognized in the pons, medulla and cord.

Microscopical examination of the tissues reveals the following positive findings:

Lungs: The alveoli are emphysematous. There are diffuse patches of fresh lobular pneumonia about bronchi filled with an exudate of leucocytes.

Spleen: Groups of the large mononuclear cells, characteristic of acute splenic tumor, are seen in the pulp.

Femur marrow: There are hyperplastic islands of blood-forming cells.

Thyroid: There is a small adenoma composed of foetal-like acini containing very little colloid.

Stomach: The subperitoneal nodule is now seen to be a calcified myoma; the purple nodules are submucous haemangiomata. No areas of ulceration are found

in the sections, but there is everywhere in the mucosa an intense mononuclear cell infiltration, consisting mostly of plasma cells. Some eosinophils are present, but there are none of the large cells to be described in the muscles.

Rectum: The mucosa is infiltrated with mononuclear cells; in one small area there is a patch of diphtheritic exudate.

Kidneys: Patches of interstitial round cell infiltration with associated glomerular scarring and collapsed tubules explain the gross cortical roughening. The pelvis is infiltrated with mononuclear cells, small lymphocytes for the most part. There is a similar mononuclear cell infiltration in the submucosa of the bladder wall and prostatic urethra.

Muscles: Sections of the rectus abdominis and psoas muscles show a most surprising change. What in the gross appeared as gray tissue, interrupting muscle bundles, is actually an intense infiltration of mononuclear cells. Lymphocytes and macrophages are present and form dense accumulations which have destroyed muscle fibres over large areas. Occasionally a few isolated hyaline fibres remain to show the earlier nature of such an area. In other places there are more normal looking muscle fibres infiltrated by smaller accumulations of mononuclear cells. Here the infiltrated muscle is still alive but is obviously undergoing destruction, as its fibres show all degrees of hyalinization. In these smaller foci of infiltration, polymorphonuclear leucocytes are also found, indicating, perhaps, that this is an earlier stage of an inflammatory reaction that would later resemble the larger areas of completely mononuclear cell infiltration. The entire picture is that of an intense inflammatory reaction associated with the death of muscle fibres.

Brain: Sections of the brain were taken from the Rolandic areas of the frontal lobes; from the temporosphenoidal cortex; from the Hippocampic region of the occipital lobes; through the basal ganglia and internal capsule; through the cerebral peduncle and pons; and through several levels of medulla. Several sections were also made of the cervical cord. In all parts of the gray and white matter of the brain, there is a most extreme and extensive encephalitis with an intense mononuclear cell infiltration and destruction of nerve cells and fibres in these areas. Some small blood vessels are made conspicuous by cuffing with mantles of these mononuclear cells, while others are not sharply outlined since the perivascular infiltration is continuous with that in the surrounding tissue. The shadowy remnants of the necrotic ganglion cells are still visible in such an area. Only a few polymorphonuclear leucocytes are present; ordinary lymphocytes are most numerous, and there are some larger mononuclear cells as well.

This cellular infiltration occurs in small patches with areas of normal tissue between, and also in larger zones, the most extensive of which are found in the pons where they were not even visible in the gross material. Small lesions are also found in the cervical cord and in the choroid plexus. The meninges show a surprising freedom from inflammation in the face of such extensive change in the brain substance; even where the lesions are quite near to the meninges, the overlying meninges may be practically normal. In one place a blood vessel surrounded

by a mantle of mononuclear cells extends into the meninges and the cells here do extend along them into the meningeal spaces; and in many other places there are scatterings of mononuclear cells in the meshes of the meninges; but there is always a marked discrepancy between the amount of meningitis and the extraordinary encephalitis. Frozen sections stained to demonstrate the myelin sheaths show no areas of disintegration or destruction except in the areas of acute encephalitis. No scarring, such as could have been caused by an earlier process is demonstrable. Nor are there any secondary areas of degeneration in the spinal cord tracts. This entire change seems definitely to be due to a recent extreme and fulminating process. The only other microscopic cerebral change is the shrinkage and narrowing of all of the zones of cortical gray matter even where there is freedom from the inflammatory change.

Eyes: Retinae normal. No change is recognizable in optic discs or optic nerves.

Ears: Blocks taken from the middle and inner ears are being decalcified by the Otology Department, and are to be studied by them in serial sections. No detailed report is available as yet, beyond the note that the drums are intact but slightly retracted, and that there is slight general atrophy of the tissue.

Bacteriology: Heart's blood—sterile. Bacterial stains of muscles and brain reveal no organisms. Levaditi stains show no spirochaetes.

DISCUSSION

The etiology of the condition is completely obscure. Even an accurate knowledge of the date of onset and duration of the illness is lacking because of the incomplete and indefinite history. It is therefore difficult to date the pathological picture or to correlate it with the clinical story. The encephalitis is recent and probably extends back no further than the vague "bad spell" which occurred a month before death. The cortical atrophy is extreme for the slight amount of cerebral arteriosclerosis, and it is unlikely that it had a share in the production of any of the manifestations of the longer illness. Nor could the remarkable muscle lesions form the basis of the long drawn out clinical picture of progressive muscular weakness, for they, too, are of recent origin.

In view of the widespread inflammatory nature of the cerebral lesion, it seems remarkable that the patient's temperature and leucocyte count were almost normal on admission and until after the spinal air injection. The absence of any change in the spinal fluid is easily understood because of the approximately normal appearance of the meninges where the finding of excess cells was rare indeed.

Nothing in the clinical history gives any indication of the nature of the extreme encephalitis. It is, therefore, only possible to surmise its cause. It differs microscopically from an acute encephalitis lethargica not in the cells present, but rather in the intensity of the reaction which is not equalled by any case in the files of the Pathological Department of this hospital. Minute haemorrhages, usually so striking in encephalitis lethargica, are lacking here. The condition may, therefore, represent an extreme degree of polioencephalitis from Virus B or some hitherto unrecognized infection. The possibility that this may be a fulminating acute multiple sclerosis must also be considered, but the amount of lymphocytic and inflammatory reaction and the absence of any neuroglial change are surely extraordinary for multiple sclerosis. Likewise the lack of any areas of demyelinization or degeneration excludes any possible confusion with the picture seen in Shilder's disease. Because there was no clinical indication of encephalitis, no bacteriological or experimental studies were made with the spinal fluid or cerebral tissue, as an aid in diagnosis.

The etiology of the muscle change is similarly obscure. It is undoubtedly of an inflammatory nature, but the profuseness of the cells is very difficult to understand because there are far greater infiltrations here than one would expect simply as a result of death of muscle fibres. The lack of muscle atrophy as well as the presence of the extreme mononuclear cell infiltration exclude any relationship to the frequently described group of chronic progressive muscular atrophy associated with disease of the central or peripheral nervous system. The completely different clinical history further differentiates this from the latter group of cases, whereas in Sättele's case it was the clinical history rather than the pathological picture of polymyositis that served to classify it as a peculiar type of progressive muscular dystrophy.

Whether, in this case, two independent conditions exist in the muscles and brain to account for the peculiar long drawn out clinical illness, or whether the lesions are related and caused by the same obscure etiological factor, it is impossible to determine. The case is reported because it seems to be unique.

SUMMARY

A case is reported which was characterized clinically by deafness and weakness of the legs for a period of ten years. A month before death, there was intensification of these and other symptoms and the addition of marked speech difficulty. Death followed a diagnostic spinal air injection. An autopsy, psoas and rectus abdominis muscles showed interruptions by an infiltrating gray tissue; the brain showed cortical atrophy, and throughout its tissue there were numerous patches of fresh yellow and red necroses. Microscopically, the muscle lesion consisted of intense chronic inflammatory change replacing large zones of muscle fibres; the brain lesions were an intense encephalitis and atrophy. The etiology of both the myositis and the encephalitis is unknown.

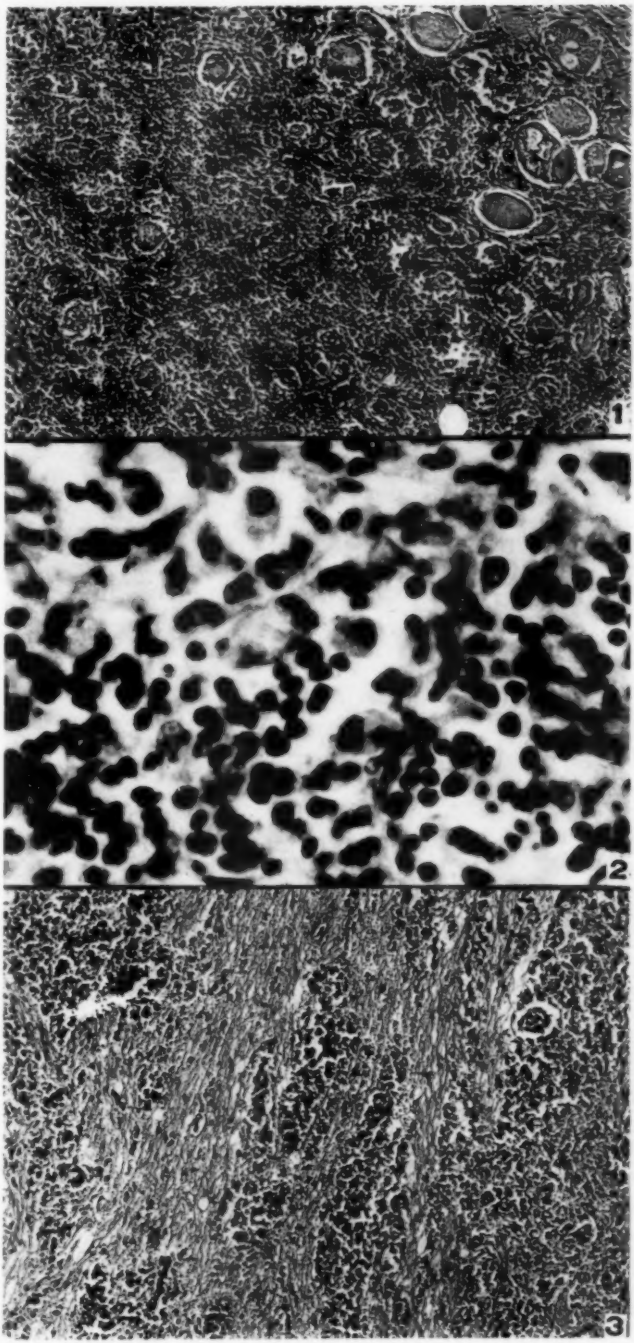
PLATE 1

(Photographs by Mr. Milton Kougl)

FIG. 1. Section of psoas muscle (×100) showing a large zone of infiltrating cells which have replaced muscle fibres. Several isolated muscle fibres, partly hyalinized, can still be seen.

FIG. 2. A higher magnification (×670) of the above, showing the dual nature of the infiltrating cells. Small lymphocytes are most numerous but large macrophages are also present. There are no muscle fibres in this field.

FIG. 3. Section of pons, showing the extreme encephalitis. Two arterioles are conspicuous because of their cuffing by mantles of mononuclear cells.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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN. Sixth Edition. Revised. 707 pp. Illus. $7.00. (*Lea & Febiger, Philadelphia, 1937*)

In his preface, Dr. Joslin justifies the need for this new edition of his book by his belief that protamine insulin is ushering in for the diabetic a new and better epoch—the Hagedorn Era. Two chapters devoted to treatment with protamine insulin are added to this book and many other additions and revisions of the text have been made. As it stands today, this is an excellent book on everything dealing with the treatment of diabetes mellitus. The author gives full credit to Dr. Howard F. Root, Dr. Priscilla White, and Dr. Alexander Marble for help in assembling the facts and writing the text. It not only encompasses the treatment of diabetes mellitus and its complications, but it also serves as an accurate reference book for most of the modern clinical and experimental work dealing with glucose metabolism.

Various workers who are particularly interested in the treatment of diabetes may not entirely agree with Dr. Joslin in his extreme enthusiasm over protamine insulin. However, his large experience with its use, (1200 cases), gives authority to his views, and he takes pains to enumerate ten of the cases which "have had difficulties with protamine insulin and either are not satisfactorily stabilized or have returned, at least temporarily, to regular insulin." Of these patients he says, for instance: "Case B has often told me that he could change his insulin by half a unit on retiring and thus bring on a reaction or make his urine sugar-free the next morning. Case F is an insulin sensitive diabetic and for years has been troubled with serious reactions. Case I teaches dancing and must adjust insulin according to the amount of her classwork."

The warning he issues is "Moral for the young doctor: 'Don't attempt to teach an old dog or a dog with established habits new tricks, especially when you can't see him often!' "

Directions for the technique of shifting from regular insulin to protamine insulin seem to the reviewer to be unnecessarily complicated and not as satisfactory as those recommended by Wilder. The very small percentage of patients who are abnormally sensitive to regular insulin are apt to be abnormally sensitive to protamine insulin also. It is clear that such patients should be handled only by physicians who have had experience in regulating difficult diabetic patients.

One cannot help being impressed by the wide personal experience and wealth

of material which for many years has been carefully recorded and analyzed. This book should be at hand for all physicians who treat diabetics and for students studying the disease.

H. M. T., Jr.

Preoperative and Postoperative Treatment. By Robert L. Mason. 495 pp. Illus. $6.00. (*W. B. Saunders Co., Philadelphia, 1937.*)

This volume has been gotten up by one of the assistants in surgery at the Massachusetts General Hospital, and on the whole it is an extremely satisfactory book. Dr. Mason brings together a great many facts that are scattered about or entirely omitted from the ordinary textbook of surgery. The book is full of informative data that one usually learns by practice but which students and interns should be familiar with before taking charge of patients. It is not entirely the work of one author, but some ten or twelve Boston specialists have contributed chapters covering the preoperative and postoperative care of patients in their special fields. This adds appreciably to the value of the work. There is another feature which deserves commendation and that is the prominence given to physiological facts as they apply to surgical conditions. One or two chapters are disappointing, particularly the one on shock, which is covered in less than four pages. The author has seen to it that at the end of the discussion of each subject there is a fairly full bibliography. One can certainly recommend this book to students and house officers interested in surgery.

W. M. F.

National Health Series, Funk and Wagnalls Company, New York, 1937. 35 cents each, or three for $1.00.

Taking Care of your Heart. By T. Stuart Hart. 110 pp.
Venereal Diseases. By William Freeman Snow. 98 pp.
How to Sleep and Rest Better. By Donald A. Laird. 83 pp. Illus.
Exercise and Health. By Jesse Feiring Williams. 70 pp. Illus.
The Common Cold. By Wilson G. Smillie. 77 pp. Illus.
The Common Health. By James A. Tobey. 96 pp.
The Healthy Child. By Henry L. K. Shaw. 108 pp.
The Expectant Mother and her Baby. By Robert L. DeNormandie. 89 pp.
Adolescence. By Maurice A. Bigelow. 99 pp.
What you should Know about Eyes. By F. Park Lewis. 82 pp.

The National Health Series, a group of volumes, some new, others revised, aims to provide "twenty short books that would give to lay readers helpful and authoritative information about various aspects of personal and community health with which they should be familiar."

Most of the books are well written in an easy, understandable fashion and without exception each presents its subject matter lucidly and adequately. "Taking Care of Your Heart" and "Venereal Diseases" merit particular praise.

The series is a really valuable contribution to the source of medical literature to be read with profit by the non-professional public.

C. R. A.

Post-Mortem Appearances. By JOAN M. ROSS. 3rd ed. 243 pp. $2.50. (*Oxford Medical Publications, Oxford University Press, New York and London, 1937.*)

This pocket-sized book, which is now in its third edition, describes the various gross pathological changes met with in the autopsy room. It is clearly written and has an adequate index. It can be recommended as a useful aid to the student who is beginning the study of pathology.

R. W. F., JR.

Précis de Physiothérapie Clinique. By PAUL DUHEM. 603 pp. Illus. 130 fr. (*Gauthier-Villars, Paris, 1937.*)

In France, as elsewhere, there has been a greatly increased interest in physical therapy in recent years. Professor Harvier in a preface to this book states that it is the first general work of its type to be published. (Presumably he meant the first one in the French language.)

The author has done a thorough job in an agreeable way. He takes up first the various modalities used in physical therapy and then special parts of the body, with a brief classification of the diseased states considered and short clinical descriptions that are very well done. He pays particular attention to diseases of the nervous system and of nutrition, those in which no doubt he has been especially interested.

Where his experience has been ample his exposition is critical enough, but in places he quotes astonishing statements by other authors with no attempt at criticism.

The reader will find many features of interest, including the national differences in points of view, in classification of disease and in the emphasis upon diatheses.

T. P. S.

Operative Surgery. By ALEXANDER MILES and D. P. D. WILKIE. 2nd ed. 631 pp. Illus. (*Oxford Medical Publications, Oxford University Press, London, 1936.*)

This volume, reflecting as it does the surgical practice at the Edinburgh School, must of necessity be of particular value to students and graduates of that distinguished institution. The authors, after enlisting the help of seventeen of their colleagues, have presented a concise and yet remarkably complete, authoritative, treatise. The illustrations are numerous and clear. Many of the chapters have a practical anatomical introduction which in some cases seems to be unduly long, so that in this connection it may be questioned whether the book is well balanced. From an American viewpoint it would seem, for instance, that too much space is

devoted to the ligation of large arteries and too little attention is given to the description of a good tendon suture. Possibly, also, some of the topographical anatomy might profitably be sacrificed for a well chosen bibliography which the house surgeons and young graduates in practice might readily consult in order to learn such details as this volume is not expected to supply. By avoiding the presentation of alternative operative measures the authors have achieved clearness and simplicity. All in all, in spite of its relatively small size, this volume can be read with profit by any one interested in the practice of surgery.

F. C. L.

BOOKS RECEIVED FOR REVIEW

National Health Series, Funk and Wagnalls Company, New York, 1937. 35 cents each, or three for $1.00.

Cancer. By FRANCIS CARTER WOOD. 102 pp.

Diabetes. By JAMES RALPH SCOTT. 132 pp.

Food for Health's Sake. By LUCY H. GILLETT. 74 pp.

Hear Better. By HUGH GRANT ROWELL. 83 pp.

Love and Marriage. By THOMAS WALTON GALLOWAY. 102 pp.

Tuberculosis. , By H. E. KLEINSCHMIDT. 77 pp.

Why the Teeth? By LEROY M. S. MINER. 71 pp.

Your Mind and You. By GEORGE K. PRATT. 126 pp.

Staying Young beyond your Years. By HOWARD W. HAGGARD. 89 pp.

The Human Body. By THURMAN B. RICE. 88 pp.

Clinical Allergy. By LOUIS TUFT. 711 pp. Illus. $8.00. W. B. Saunders Company, Philadelphia & London, 1937.

Health Education of the Public. By W. W. BAUER and THOMAS G. HULL. 227 pp. Illus. $2.50. W. B. Saunders Company, Philadelphia & London, 1937.

The Patient and the Weather. Vol. 4, part 1. Organic Disease. Cardio-vascular-renal Disease. By WILLIAM F. PETERSEN. 663 pp. Illus. $10.00. Edwards Brothers, Ann Arbor, Mich., 1937.

Dextrose Therapy in Everyday Practice. By E. MARTIN. 451 pp. Illus. $3.00. Paul B. Hoeber, New York, 1937.

Safely through Childbirth. By A. J. RONGY. 192 pp. Illus. $2.00. Emerson Books, Inc., New York, 1937.

Childbirth: Yesterday and Today. By A. J. RONGY. 192 pp. Illus. $2.00. Emerson Books, Inc., New York, 1937.

An Investigation into Questions of Social Hygiene in the Counties of Västerbotten and Norrbotten, Sweden. Conducted with the support of the Royal Medical Board in 1929–1931. Published in Swedish in 1934. English, partly revised, edition, 691 pp. Illus. Hakan Ohlsson, Lund, 1937.

5

LESIONS OF THE RECTUS ABDOMINIS MUSCLE SIMULATING AN ACUTE INTRA-ABDOMINAL CONDITION

THOMAS S. CULLEN AND MAX BRÖDEL

From the Departments of Gynecology and of Art Applied to Medicine, The Johns Hopkins Medical School

I. ANATOMY OF THE RECTUS MUSCLE*

MAX BRÖDEL

Although hyaline degeneration of muscle fibers following acute infectious diseases takes place in other regions of the body, it seems to occur more frequently in the rectus abdominis. There probably is good reason for this and it is hoped that the following study will throw some light on the subject. The blood supply seems to be of special interest, for it is hard to believe that destruction of muscle and consequent rupture could occur without previous disturbance of its vascularization. The rectus differs in construction and vascularization from other muscles; also in regard to the vulnerability of its lower portion to mild or severe infections, originating in the abdominal viscera or in the general blood stream. A careful study of the anatomical literature revealed the singular fact that the subject is usually treated superficially, both in regard to text and illustrations. This was probably because it seemed such a simple matter and yet there are a number of obscure points about the rectus which made it necessary for the illustrator to dissect, inject and section

*My friend, Max Brödel, has long been interested in the anatomy of the rectus abdominis muscle and kindly offered to make one or two illustrations for my article on hemorrhage into the rectus. As the months went by he delved more and more into the anatomy and histology of this muscle. His studies were so interesting that I could not for a moment think of incorporating them in my clinical article when, as a matter of fact, the credit belongs solely to him. After much persuasion he consented to publish his Anatomy of the Rectus Abdominis Muscle.

Max Brödel and I have been most closely associated since 1894, and it is an honor and a pleasure to have my name linked with his in this short monograph.

T. S. C.

many specimens before it was possible to make the drawings. The result of these studies is set forth in the following pages.

The form of the abdominal wall varies greatly according to sex, age, constitution, state of nutrition and posture of the individual. These factors greatly affect the size, shape and muscular tone of the rectus. In an asthenic individual in the horizontal position it hangs

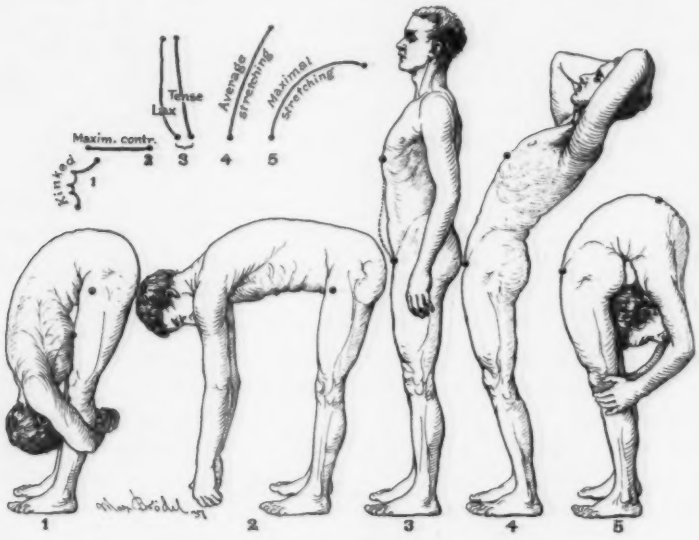

FIG. 1. THE RECTUS MUSCLE IN FIVE POSITIONS OF THE BODY

(1) Maximally contracted and kinked (acrobat); (2) maximally contracted and straight; (3) erect posture, lax and tense; (4) average stretching; (5) maximally stretched (acrobat).

hammock-like toward the lumbar vertebrae. In a stout individual in the erect position it bulges forward and is considerably elongated, especially during forced inspiration. A permanently stretched rectus cannot contract as vigorously as the rectus of a young athlete, which runs in a straight line from ensiform to symphysis (fig. 1). Since the rectus is one of the muscles concerned in regulating the so-called intra-abdominal pressure and in acting, together with others, as a

muscle of expiration, it cannot be strictly considered to be in a state of rest, at least while the body is in the erect posture. Great exertion is demanded of the muscle when the body is raised from the horizontal to the sitting posture without the aid of the arms, also by violent coughing and the strain of defecation.

In maximal contraction muscles are said to shorten down to one half their length. This is probably too high a figure, at least for most of them. The involuntary muscles are capable of much greater contraction than the skeletal groups. The rectus of an athletic youth probably can contract no more than 17 cm., which quite agrees with Leonardo's 9-fingers' width. If ensiform and symphysis are brought still closer together, the rectus becomes kinked at the umbilicus and midepigastrium (fig. 1).

That a healthy muscle can be stretched enormously without injury is demonstrated by acrobats and dancers. An abdominal tumor, excessive obesity, ascites or a pregnant uterus can easily elongate a rectus to twice its length and almost twice its width.

It may be of interest here to present a free translation of the quaint description of the rectus by the great painter, sculptor, architect, scientist, musician and anatomist Leonardo da Vinci (1452–1519).[1]

"There is a long muscle in front of the abdomen, running from the ensiform process to the symphysis pubis. Its contractile force is divided into three parts, for it is divided by three transverse tendons into three separate smaller muscles."

[Leonardo left out the inconstant tendon between umbilicus and symphysis. He also should have known that three tendons divide the rectus not into three, but four muscle bellies.]

"It is the business of this great muscle during flexion and extension of the trunk to stretch as much as 9-fingers' width and then again to contract by the same amount. Nature certainly displayed fine judgement and esthetic sense when it divided this long and powerful muscle into several sections. Had the muscle been built of one piece (like the bulging biceps of the athlete) it would in a state of maximum contraction produce a most unsightly swelling in the region of the

[1] Trattato della Pittura: from the Codex Vaticanus 1270 (German translation by Heinrich Ludwig: brother of the great physiologist Carl Ludwig) Wien, 1882, s. 153–4.

navel. The beauty of the human body therefore is greatly enhanced by this division of the rectus muscle into three separate smaller portions, none of which can bulge very markedly, even in the state of maximum contraction, when the muscle becomes shorter by 9-fingers' width."

Origin and insertion: Because the pelvis is more centrally located than the costal cartilages and the principal function of the muscle is to bring the sternum toward the symphysis, to regulate or increase the intra-abdominal pressure and also to act as a muscle of expiration, the lower end should be referred to as origin, the upper as insertion. Moreover, in rupture of the muscle the symphysial end would have to be regarded as the fixed point. In the anatomical literature, however the rectus has always been described from above down and here the usual custom will be followed.

Figs. 3, 4 and 9 show the rectus arising above from the under surfaces of the 5th, 6th, and 7th costal cartilages, the xiphoid process and costoxiphoid ligament. These bundles are of unequal width and soon merge into a broad, thin muscle which continues with three or four tendinous interruptions downward to its tendinous insertion into the superior pubic ramus and the symphysis pubis.

The upper or thoracic portion ends in the first transverse tendinous band approximately paralleling the costal margin. From this arises the next muscular mass, square in shape, which terminates in the second transverse tendon, about midway between the costal margin and the umbilicus. The third muscle-mass also is square in form and ends in the third and last transverse tendon at the level of the umbilicus, sometimes a little above or below. The fourth muscle mass from umbilicus to pubis is the longest and thickest, becoming narrow below and terminating abruptly in a short, strong tendon, attached to the upper surface of the pubic bone and cartilage.

Approximately at the level of the semicircular line of Douglas, 3.5 to 5 cm. below the umbilicus, we occasionally find another transverse tendon, usually incomplete, dividing this long lower segment into a small upper square portion and a lower, powerful, triangular, symphysial portion. We thus find the entire rectus muscle divided by three (or four) strong transverse tendons into four (or five) independent muscular masses, each of which has its own motor nerve supply.

They are served, however, by only one common vascular system, fed from above and below.

The origin of the muscle from the 18th to the 25th myotomes of the early embryo suggests the possibility that the tendinous inscriptions between the myotomes might be identical with the tendinous inscriptions in the adult rectus. There is however no evidence that this is the case. The inscriptions begin to disappear in the 11 mm. embryo and the myotomes fuse into one continuous column from above down, and when the primitive rectus has shifted from its original position at the lateral body wall to the ventral position, no tendinous inscriptions can be demonstrated in it anywhere. They must therefore be regarded as of subsequent origin.

The sheath (figs. 2, 8 and 9). The rectus muscle is encased in a strong sheath, formed through fusion of the flat tendons of the three broad abdominal muscles: external oblique, internal oblique and transversus abdominis. At its lateral margin, the semilunar line [Spigeli], the sheath has from 5 to 8 perforations, through which the intercostal nerves and vessels enter. The intervals between these foramina are often irregular.

The *anterior leaf* of this sheath covers the entire ventral surface of the rectus. It is stronger below than above. While the upper part of the leaf consists of only the external oblique tendon and a half of the internal oblique tendon, the lower part is made up of the union of all the tendons, of both oblique muscles, plus the tendon of the transversus. The anterior leaf is intimately adherent to all the transverse tendinous intersections, and also to the lateral and mesial margins of the muscle. This produces tight compartments, each filled by its muscle belly. In vigorous contraction the bulging muscle masses are made still more conspicuous by the depressions of the transverse tendinous intersections.

The *posterior leaf* consists of the flat tendons of the transversus muscle and of the posterior half of the internal oblique tendon. It is shorter than the anterior leaf and ends in the linea semicircularis [Douglasi] about 5 cm. below the level of the umbilicus. Below that line the rectus muscle has no sheath covering it. The lower tapering part of the rectus, which is the strongest portion of the muscle, is separated from the abdominal viscera by only the thin and filmy

peritoneum, reenforced by the thin layers of subperitoneal and transversalis fascia (figs. 2 and 8). The posterior leaf of the rectus sheath is strengthened above by the transversus muscle. In the angle between ensiform process and seventh costal cartilage it is pierced by the superior epigastric vessels. It is free all the way down to Doug-

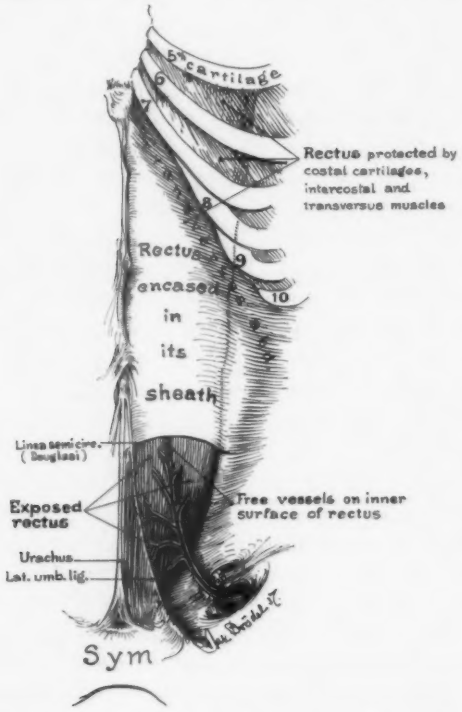

FIG. 2. VULNERABILITY OF DORSAL SURFACE OF LOWER RECTUS

las' line and not adherent to the rectus at any point. The contracting and relaxing muscle can move freely up and down, and on this mobile muscle surface, quite loosely attached to it, runs the large inferior epigastric artery with its two accompanying veins. In their lower part these big vessels are separated from the abdominal viscera by only the delicate peritoneum and a thin fascia.

THE MUSCLE

The entire muscular mass of the rectus in the adult is 35 cm. long, 7 cm. wide and 0.8 cm. thick. There is, of course, a wide range of variations according to body length, muscular strength, race and sex. Maximum measurements are 42 x 8 x 1, the minimum

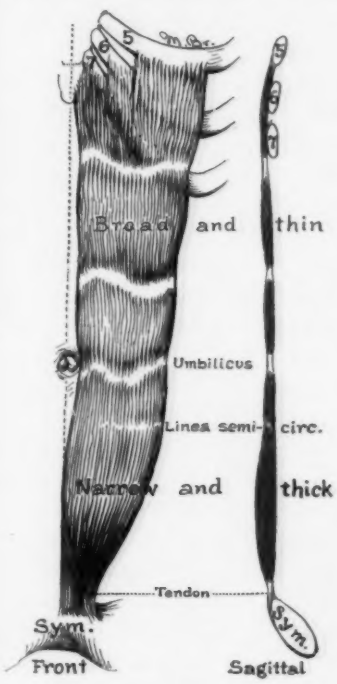

FIG. 3

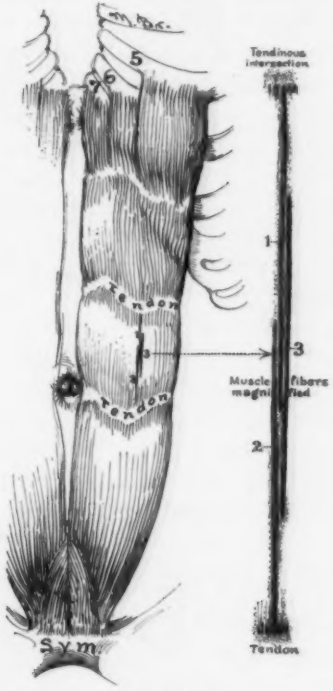

FIG. 4

FIG. 3. GENERAL TOPOGRAPHY OF MUSCLE MASS
FIG. 4. DIAGRAM, SHOWING LENGTH OF MUSCLE FIBERS

30 x 6 x 0.5. This mass is divided by tendinous intersections into four or five separate muscles. The upper are square and relatively thin; the lower is long, narrow below, and thick (figs. 3 and 9).

The individual muscle fibers are quite short, rarely long enough to reach from tendon to tendon. 4 cm. is considered their maximal

length, although in very long muscles fibers of 10 cm. or more may be found. It is therefore likely that the muscle bellies of the rectus contain the usual three types of fibers (fig. 4), beginning in tendon above and ending in muscle, beginning in muscle above and ending in tendon below, or beginning in muscle and ending in muscle. Each muscle fiber is encased in its delicate sarcolemma sheath, which at the two poles is firmly attached to the perimysial connective-tissue framework of the muscle, or to the tendon (fig. 5).

On naked-eye inspection the muscle can be demonstrated as composed of parallel muscle bundles of the *first order*, measuring on the average 5 mm. in diameter (figs. 6 and 7). Maximum in strongly developed individuals, 6 mm., minimum in weaker bodies 3 mm. The muscle bundles are easily separated by blunt dissection, either in fresh or hardened material without damage to either muscle, vessels or nerves. On section they are triangular, square, rhomboid, pentagonal, mostly without any definite pattern. The spaces between the large muscle bundles contain an elaborate system of vessels, nerves and lymphatics supported by a dense network of connective-tissue fibers. This is continuous with the sarcolemma of the muscle fibers. The vessels and nerves possess considerable mobility within these chinks. Their direction is at right angles, or nearly so, to the muscle bundles. Later on they will be described more in detail.

The bundles of the first order are composed of parallel bundles of the *second order*, measuring about 0.8 mm. in diameter (figs. 6 and 7). Each of them again is made up of parallel muscle fibers of an average diameter of 0.05 mm. (50 μ) or 7 to 10 times the width of a capillary. The fiber is thicker in old age and in muscular individuals. This minute mass of muscle structure is encased in a sarcolemma sheath of great delicacy (0.001 mm.). The nuclei of the muscle fiber are situated in the periphery of the sarcoplasm just under the sarcolemma sheath. Their number varies according to the length of the fiber. Long fibers have several hundreds of them scattered irregularly over their entire length. The sarcoplasm of the fiber consists of a bundle of delicate parallel fibrils showing the characteristic striation of voluntary muscle. Each fibril is about 1 to 2μ in diameter (fig. 5). During the embryonic growth of muscle the fibers are seen to multiply at an enormous rate. The maximum

number appears to be reached at birth; they then begin to decrease in number. Many fibers degenerate through vascular changes which apparently is a normal process of adjustment in post-fetal muscle

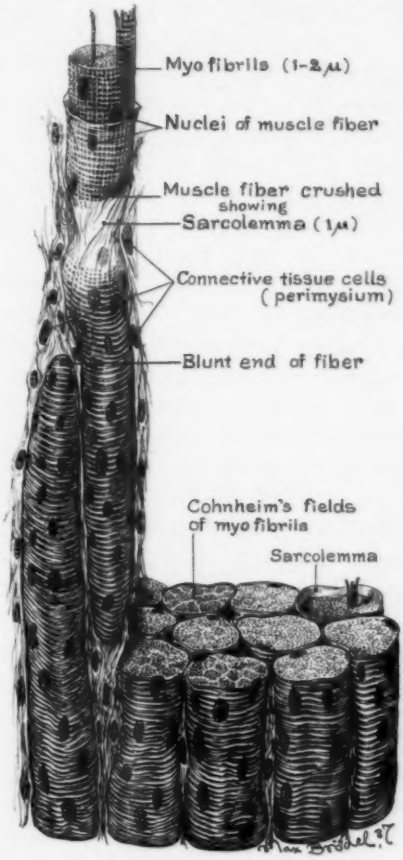

FIG. 5. SCHEMATIC REPRESENTATION OF FINER STRUCTURE OF MUSCLE FIBERS

growth. The surviving fibers are being favored by the developing permanent blood supply, as a consequence of which they increase in length and thickness as the body grows.

THE NERVES

The rectus has a multiple nerve supply. It comes from the ventral branches of the fifth to the twelfth thoracic nerves and occasionally also from the first lumbar nerve. They enter the muscle at fairly regular intervals, but are apt to be subject to numerous variations in regard to end-distribution.

When in the embryo the rectus pushes forward from the myotomes of the mesoderm, it has already been invaded by the ventral twigs of the spinal nerves, which it carries along on its journey toward the umbilical cord. The latter is so large in caliber that the two recti are forced to remain widely separated during the greater part of intra-uterine life.

The motor and sensory nerves usually run together as common trunks between the internal oblique and transversus muscles until about 1 to 3 cm. from the semilunar line, where they divide. They pierce the rectus sheath at the semilunar line either separately or in groups, usually accompanied by the rather insignificant terminal branches of the lower intercostal vessels (figs. 7 and 8). The 5th to the 9th intercostal nerves supply the upper portion of the rectus down to the umbilicus. The 10th usually runs to the muscle field above, at or just below the umbilicus, while the 11th, 12th and ilio-hypogastric, or upper branch of the first lumbar nerve, take care of the lower, stronger tapering portion of the rectus.

Having penetrated the sheath, both the motor and sensory bundles run transversely across the dorsal surface of the muscle. While the motor branches curve toward the muscle areas, the sensory branches are directed toward the tendinous intersections. The motor nerves spread out in fan-shaped manner. They may enter the muscle body anywhere, but usually do so at or near the main trunk of the epigastric artery (figs. 7 and 8). Inside the muscle body the fan-shaped radiation of the motor bundles becomes marked. They usually accompany one of the larger oblique epigastric branches and cross the muscle bundles at angles varying from 45° to 90°.

The sensory twigs run along the dorsal surface of the tendinous band and send short perforating branches through it to the skin at intervals of 0.5 to 1 cm. While this seems to be the rule, sensory nerves may also follow the course of the motor branches and emerge

from the muscle field together with cutaneous vessels. In either case the distribution in the skin is the same—directed obliquely downward and mesially. It would be redundant to describe the end distribution of the nerves in this study.

THE VESSELS (FIGS. 2, 6, 7, 8, AND 9)

The rectus muscle is supplied by two vascular systems, from below, by the inferior epigastric artery arising from the external iliac at Poupart's ligament and from above, by the superior epigastric artery, which is the terminal branch of the internal mammary. In the early embryo we find that the two sources are independent systems, travelling toward each other from opposite directions. At the midpoint between the ensiform and umbilicus they meet in an undifferentiated plexus of precapillary arterioles. There are no main arterial branches in this portion of the muscle, but we find small lateral anastomoses coming from the seventh, eighth and ninth intercostal arteries, also mesially from the umbilical circulation. In the newborn the superior and inferior epigastric arteries have joined together, through the establishment of two or three anastomosing channels in the mid-epigastric portion of the muscle, the middle branch usually becoming the main channel in the adult. Thus we have now one large continuous vessel from the subclavian artery above down to the external iliac below. This large vessel runs over the entire dorsal surface of the rectus, lying in a shallow groove, adherent to or buried in the muscle for a short distance at the umbilicus and again detached and mobile down to the external iliac. This arrangement is important in vigorous contraction and stretching of the muscle. The intercostal arteries also join the rectus circulation. After having given off many branches to the broad abdominal muscles they become greatly diminished in size and persist in the adult only as insignificant vessels, paralleling the sensory and motor nerves with which they enter the rectus sheath at its lateral border. They are the terminal ventral branches of the eighth to the twelfth intercostals and occasionally also the first lumbar. They pass over the dorsal surface of the rectus and join the main vessel near the middle of the muscle. They do so at an angle of from 45° to 60° against the direction of the inferior epigastric bloodstream, which makes it evident

that they play only a minor rôle in supplying the muscle with blood. It is more likely that the terminal branches of the intercostal vessels receive blood from the inferior epigastric artery. The entire arterial system with all its branches is paralleled by a complete double system of veins. This is true down to the smallest arteries, 50μ in diameter, each of which has its two accompanying veins. It was impossible to show them all in the illustrations.

It may be of interest to add that all the larger veins throughout the rectus are supplied with valves, the free edges of which point in the direction of the bloodflow. They are always found distal to the larger tributaries entering the vein. At the mid-epigastric level the valves change their direction making the upper third of the rectus drain upward into the subclavian and superior vena cava, the lower two thirds downward into the external iliac and inferior vena cava (fig. 6e).

Fig. 6, dorsal view, pictures the average rectus circulation. It is evident that the blood stream has the choice of flowing either from the internal mammary down or, from the inferior epigastric up. It is indeed possible to inject the entire muscle with ease in either direction, but the inferior epigastric artery seems better fitted to perform the task. There is little collateral circulation, the blood coming from the intercostals, the first lumbar and circumflex iliac playing only an insignificant rôle in the normal body, although it is quite possible for any of these collateral branches to take care of the entire rectus muscle or portions of it, should the major blood channels be temporarily or permanently blocked. The same may be true of minor collateral channels, with the parumbilical group and the two lateral umbilical ligaments (umbilical arteries) and the middle umbilical ligament (urachus, allantoic circulation).

The internal mammary artery passes down parallel to the lateral border of the sternum and gives off intercostal branches in a somewhat irregular fashion. It finally divides into two main channels of nearly equal size, the musculo-phrenic artery running laterally between the 6th and 7th costal cartilages and the superior epigastric artery, running downward and mesially across the dorsal surface of the 7th costal cartilage to the level of the lower border of the ensiform cartilage, where it perforates the posterior leaf of the rectus

sheath, here heavily reenforced by the transversus abdominis muscle. The vessel makes for the middle of the posterior surface of the

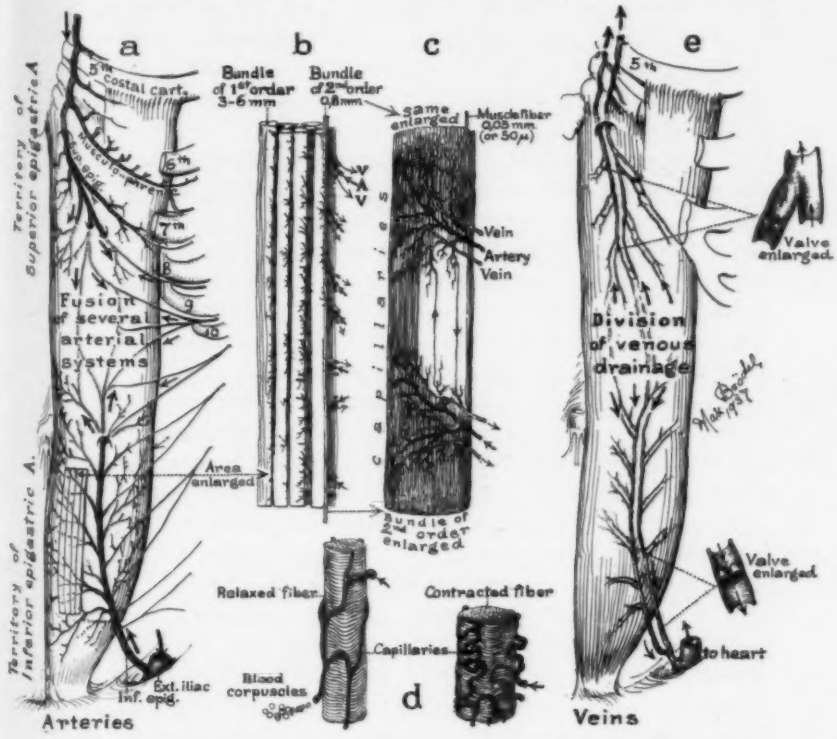

FIG. 6. DORSAL VIEW, DIAGRAM OF THE ENTIRE RECTUS CIRCULATION

(a) The main arteries feeding the muscle; (b) the smaller arteries crossing bundles of the first order, each artery has two veins; (c) the smallest arteries crossing bundles of the second order, note short arterioles breaking up into dense capillary network; (d) relaxed and contracted muscle fiber showing difference in capillary pattern, compare size of blood corpuscle (7μ) with width of narrowest capillary (5μ); (e) the main veins and the direction of the blood flow. Excepting the venules, which drain the capillary network, all veins are double.

rectus and gives off a large branch skirting the lower border of the 8th costal cartilage. It supplies a small portion of the rectus muscle

and of the transversus abdominis and joins the ventral branch of the 8th intercostal artery. The main branch of the superior epigastric remains loosely attached to the middle of the dorsal surface of the rectus but its branches plunge into the muscle usually from 1 to 2 cm. from the main trunk. About halfway to the umbilicus the artery usually digs into the body of the muscle, dividing into two or three parallel channels which again unite at about the level of the umbilicus, or slightly below. This is the region, where in the embryo the upper and lower vascularizations meet. From here on the vessel again lies on the dorsal surface of the muscle and continues in a fairly straight line down to the internal inguinal ring.

It is this last section which is of special significance in this study, for it is in this territory that muscular rupture and hematomata usually occur (figs. 2, 7 and 8). It is the field belonging to the inferior epigastric alone. The blood from the superior epigastric and from the lateral, mesial and inferior anastomoses remains a negligible factor. Figs. 2 and 6 show that the direction of the blood stream in this territory is from below upward and mesially at an angle of 45°. When the vessel has crossed the rectus border it ascends on its dorsal surface where it gradually straightens up to the perpendicular until it reaches the middle of the muscle. In its course it gives off several large branches, the lowermost of which runs down to the symphysial end of the rectus. Sometimes there are two such descending branches. They may or may not join twigs coming from the iliohypogastric branch of the first lumbar and from the allantoic and retrosymphysial vascular channels. The main artery then sends off, at intervals of 1 to 3 cm., short or long extra-muscular branches. These usually travel over the dorsal surface, often for quite a long distance before their twigs plunge into the muscle body. (They are not nearly so long in the upper rectus.) This arrangement protects the vessels in case of excessive muscular activity. They finally enter in such a manner that their branches can spread out at right angles, or nearly so, to the muscle bundles. Figs. 6, 7 and 8 show how well this arrangement is maintained throughout.

The lower rectus is the most powerful part of the muscle (fig. 3). Its change in length between excessive contraction and maximum stretching is extensive. There is only one major vessel to take care

of this long stretch of muscle and in order to avoid damage to itself, especially to its thin-walled veins, it must keep away from the muscle as far as possible and send its branches into the muscle substance in such a manner that the muscular action does not interfere with vascular freedom. (Figs. 2 and 8.) If the muscle bundles of the first order are drawn apart, as shown in fig. 7a, the characteristic arrangement of the rectus circulation becomes clear. The larger intramuscular arteries branch freely and form numerous anastomoses. They run at an angle varying from 60° to 90° to the axes of the bundles. If an occasional artery runs parallel to the muscle bundle, it shows greater tortuosity. It should be noted that the arteries crossing the bundles of the first order are usually 4 mm. apart. Occasionally they are as close together as 2mm., or as far apart as 6 mm. Each has two accompanying veins. The arteries crossing the bundles of the second order also show the transverse type (figs. 6c and 7b). They are approximately 2 mm. apart, but sometimes more or less. They give rise to short arterioles (10 to 15μ) which turn at right angles and break up into a delicate longitudinal network of parallel capillaries running up and down, three to each muscle fiber. There may be only two and again in other places as many as five. The capillaries are in intimate contact with the sarcolemma, occupying the minute triangular space which is always found where three round columns are closely packed together. It is not easy to determine which fiber is served by the capillary, but it is likely that it serves several.

The length of the capillaries varies from 1.5 to 4 mm. according to the distance between arteriole and venule. There must be a definite relationship between this measurement and the excursion of the muscle fiber between maximal contraction and maximal stretching. A capillary probably does not permit stretching beyond a certain amount. The capillaries drain into short venules (10 to 15μ) which empty into the small veins crossing the bundles of the 2nd order. It will be noted that there are always two veins accompanying each artery.

The lumina of the capillaries vary from 5 to 8μ; most of them are 7μ. There are frequent loops which are much thicker, 10 or even 15μ. It is possible that these thickenings are evidence of relaxation

of the fiber, which stretches the straight capillaries, but not the loops (figs. 6d and 7c and d).

The red blood cells with a diameter of 7μ often squeeze only with difficulty through these narrow channels. Indeed it is evident from injection studies that even in the largest capillaries there is room for the passage of only one blood cell at a time (figs. 6c, 6d and 7d).

A. Krogh[2] has shown that in the smallest capillaries the blood corpuscles have to stretch to twice their length or bend double where a capillary branches. They get much distorted, but always resume their normal shape afterwards. The flow of blood in the capillaries often becomes accelerated or retarded, sometimes stopping altogether for a while. Then the blood resumes its flow or changes to the opposite direction. It is quite common to observe stasis and temporary agglutination in clumps, blocking the flow at the venous end of the capillaries or elsewhere. This may sometimes lead to excessive distention of the channel and passage of red blood cells through a hole in the capillary wall to become deposited outside. All this happens in normal circulation.

Stasis in the minute capillary channels is effectively combated by the contraction of the muscle bundles. The contracted muscle becomes much shorter and thicker. Its parallel capillaries become tortuous and twisted (fig. 6d). Compression drives the blood into the venules and from them into the larger veins, which, aided by their valves, force the blood in the direction of the heart, acting like a pump. Muscular contraction is an important factor in promoting an active flow of blood through the muscle. The small arteries and capillaries dilate. A working muscle has much more vascular activity than a muscle at rest. When the muscle relaxes, these venules quickly fill again from the peripheral capillary bed. This suction is due to the fact that all the veins have valves, which permit blood flow in the direction of the heart only (fig. 6c and e). In spite of this effective mechanism assuring under normal conditions a continuous flow of blood through this maze of minute channels, it is known that pathological obstructions frequently may interrupt this flow. A few agglutinated blood cells, a minute microscopic thrombus might well

[2] August Krogh; The Anatomy and Physiology of Capillaries, *Silliman Lectures, Yale Univ. Press*, 1922.

cause the complete blocking of the capillary bed of a few muscle fibers and thus lead to their hyaline degeneration. It is quite likely that this happens frequently in mild acute infections or even in healthy individuals without ever being detected.

As Forbus[3] has shown, degenerated muscle fibers promptly regenerate and a few weeks later nothing may be demonstrable either clinically or microscopically unless a larger, massive group of muscle fibers has been rendered useless by hyaline degeneration. If a considerable part of the muscle substance has been destroyed through such degeneration, either in a solid block or in a diffuse manner scattered over the entire width of the muscle, it is quite conceivable that the remaining unaffected muscle substance at this level is unable to prevent rupture. The rectus is a very long muscle, composed of a number of independent sections. If the upper, more protected, portion has remained sound and capable of vigorous contraction, it may be strong enough to overstretch and finally tear apart the weakened lower portion and with it the inferior epigastric vessels or their branches where they are intimately anchored to the muscle (figs. 2, 6 and 8).

The arteries are less apt to tear than the veins, because they are far more resistant. It is difficult to tear them. They lie so loosely embedded in the intermuscular connective tissue, that they can be pulled out quite far without injury. But not so with the veins. They are frail, of smaller caliber and much thinner wall. They tear easily. Figures 2, 6 and 8 show the location of the vulnerable veins in cases of rectus rupture. The tear may be partial or complete. In a partial tear only branches of the main vessels rupture beyond their point of entrance into the muscle body, but a complete tear is apt to rupture the main trunk also. The torn edges of the muscle have been found separated by a gap 3 to 5 cm. in width.

A further discussion of this question does not belong in the anatomical section.

[3] Wiley D. Forbus: Pathologic Changes in Voluntary Muscle. *Archives of Pathology and Lab. Med.*, Sept. and Oct., 1926.

FIG. 7. (a) Dorsal view of umbilical portion of left rectus, the muscle bundles of the first order are pulled apart showing the arrangement of the blood vessels and nerves; (b) the blood supply of the bundles of the second order, arteries red, capillaries and veins black; (c) the capillary network of the muscle fibers, note thick loops crossing fibers; (d) the same in higher magnification showing size of red blood cells to establish scale.

FIG. 8. DORSAL VIEW OF ABDOMINAL WALL SHOWING THE BLOOD AND NERVE SUPPLY OF THE RECTUS MUSCLE

For the sake of clearness many of the smaller arteries and nearly all the veins have been omitted. It was evident that the simplicity of an incomplete injection is much to be preferred to the chaotic complexity of a complete injection. Note that the reverse of this page shows the front view of the same abdomen. The two pictures register to produce an instructive transparency.

FIG. 9. VENTRAL VIEW OF ABDOMINAL WALL SHOWING THE RECTUS MUSCLE, ITS CIRCULATION AND NERVE SUPPLY

Note that the reverse of this page shows the inner surface. Hold up to light and study the transparent effect.

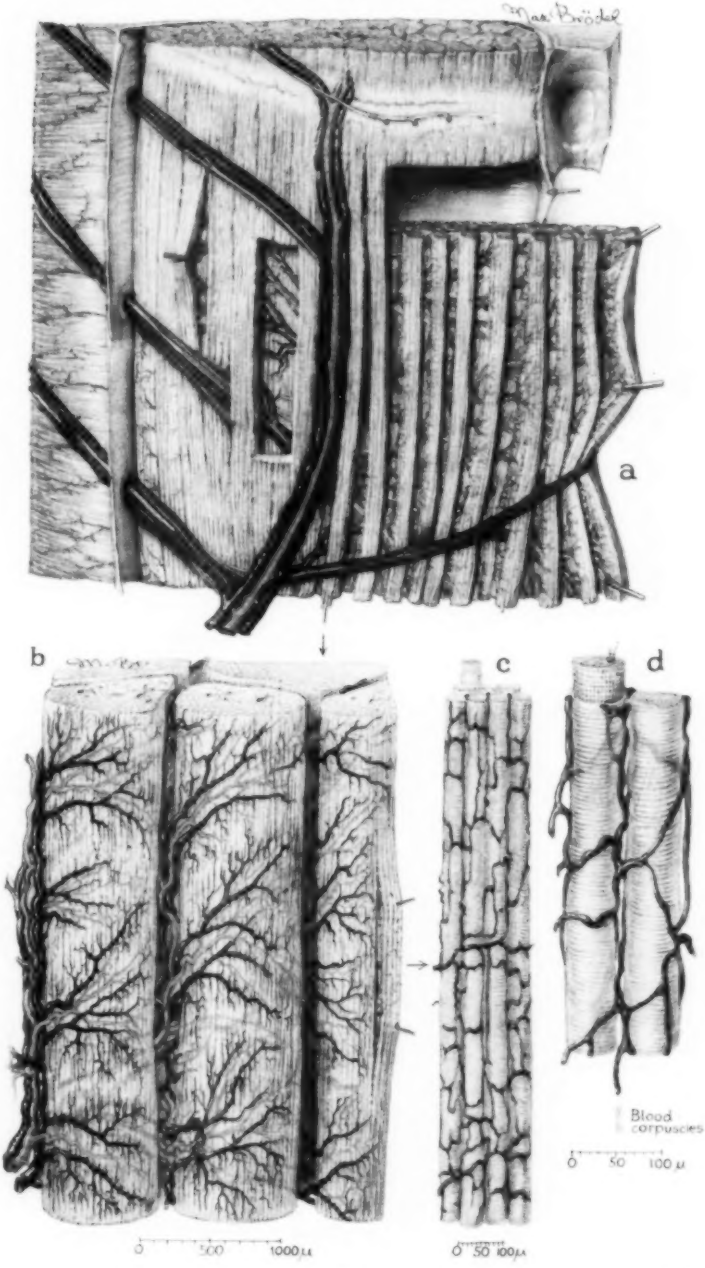

FIG. 7

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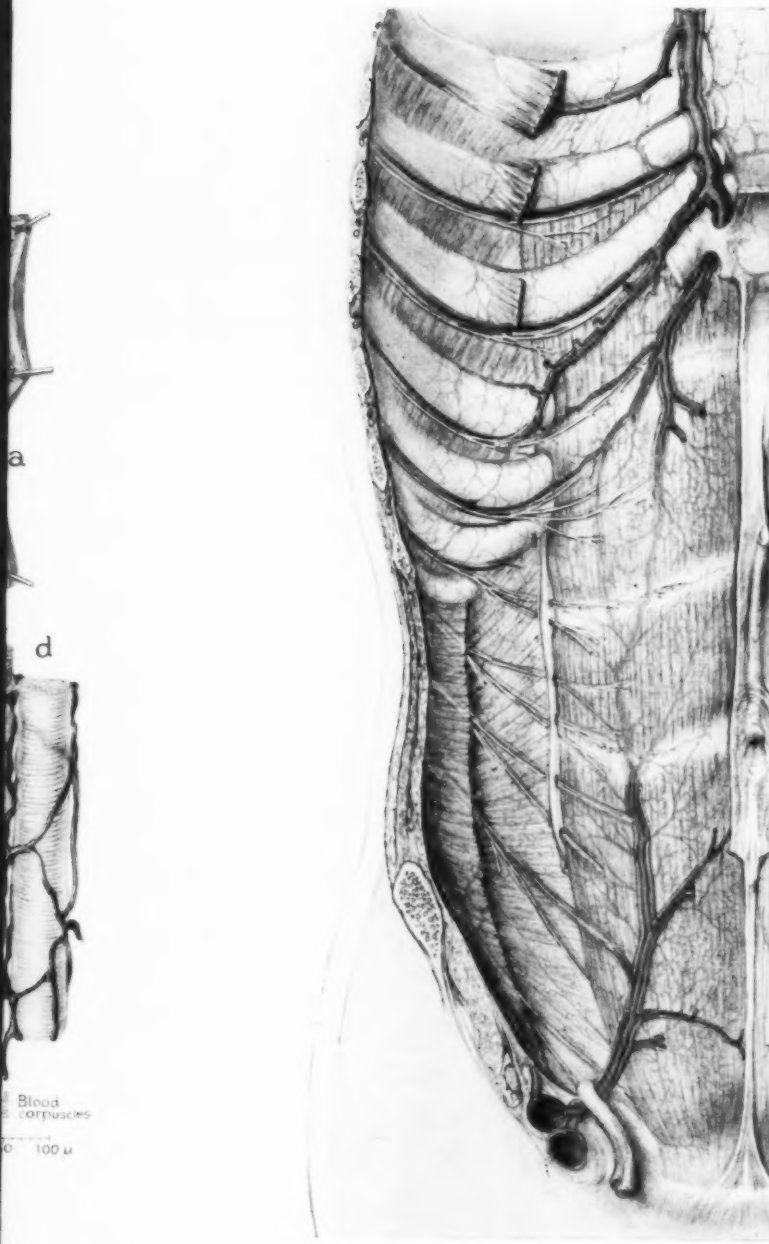

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FIG. 8

FIG. 8

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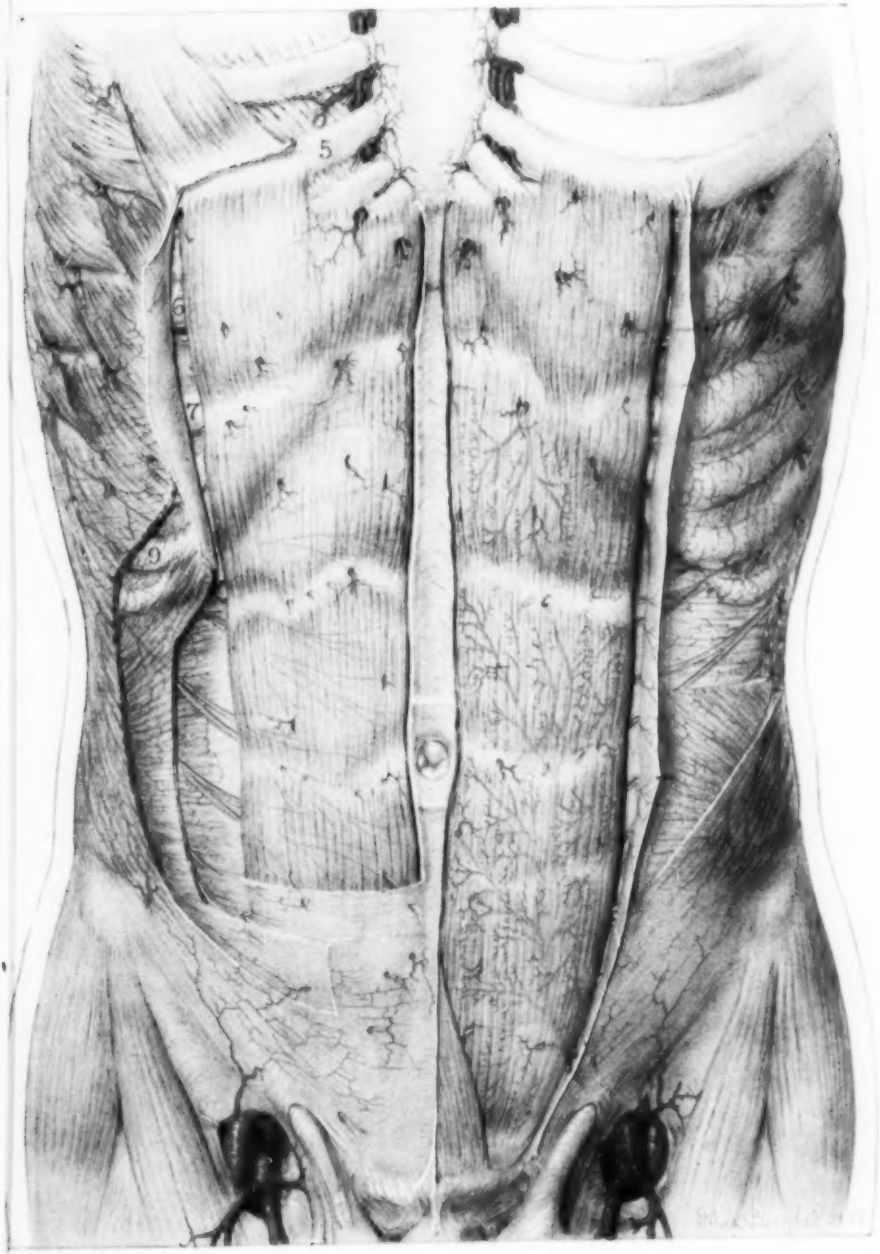

FIG. 9

II. HEMORRHAGE INTO OR BENEATH THE RECTUS MUSCLE SIMULATING AN ACUTE ABDOMINAL CONDITION

THOMAS S. CULLEN

Spontaneous hemorrhage into the abdominal wall is relatively rare. Probably one of the first cases reported in the United States was that recorded by Dr. Samuel B. Richardson, of Louisville, Kentucky. His article appeared in 1857, in the *American Journal of the Medical Sciences*. Richardson says:

"Before breakfast, and shortly after a healthy evacuation from the bowels, on Friday morning, February 29, 1856, Mr. B., a healthy athletic young man, aged 28 years, in a half playful mood, hopped over a narrow ditch. *Immediately* after this effort, he was seized with acute, persistent pain about two inches below and to the right of the umbilicus. Simultaneously with, or rather just preceding, the access of pain, he heard a distinct sound or snap, like the crack of a whip. Nausea, with a constant desire to evacuate the bowels, supervened and persisted."

Dr. Richardson saw the patient with Dr. John N. Lewis, on Saturday, March 1. "There existed a flat tumor in the region of the pain, but now much augmented in size and extent, with very marked rigidity and increased sensibility all over the abdomen.

"March 2. Patient's condition more aggravated than before; has not slept, he says, since the accident; vomiting very frequent since midnight, with constant nausea; there is a feeling of prostration with headache; tenesmus persists."

At operation the findings were as follows: "Incision brought into view a large coagulum of dark, black blood. This, upon its removal, was found to occupy an irregular cavity very like that of a diffuse, false aneurysm. It was supposed, by estimate, to weigh about half of a pound, resting and pressing posteriorly and deeply upon the peritoneum and bowels.

"The peritoneum was found uninjured, advancing forward or rising as the bloody mass was removed. Upon clearing the exposed cavity of its bloody contents, the extraordinary nature of the injury was clearly revealed. The right rectus abdominis muscle entire, with the corresponding epigastric artery and its accompanying vessels and nerves, as well as the sheath of the rectus muscle, were torn completely across, and their ends retracted and separated one and a half to two inches. The precise point of rupture was a central one between the right linea alba and linea semilunaris, and the linea transversa which intersects the umbilicus, and the linea transversa next below it.

"One artery only was tortioned—none ligated. Warm water dressings were applied."

The man made a satisfactory recovery.

Richardson says: "I have not met with a similar case to the above in my practice or reading, and I have consulted all the English and French surgical literature on the subject, contained in my moderately full library. In tome 20, *Dictionnaire de Méd.* (30 vol. edition), pp. 360–62, I find reference to such an accident, but no detailed case."

Karl Maydl, of Vienna, in 1882, wrote a most valuable series of papers on the subcutaneous tearing of muscles and tendons, and on fractures due to traction. He devotes considerable attention to the tearing of the rectus abdominis muscle and tabulates the cases. In 1913 L. S. Pilcher reported a case of spontaneous rupture of the rectus abdominis muscle. His article appeared in the *Year Book of the Pilcher Hospital*, Brooklyn. Pilcher's patient was a young man of 27, who attempted to vault upon the back of his horse. There was rupture of the right rectus. His appendix showed a chronic inflammation; it was removed. The ends of the rectus muscle were then brought together. In 1918 Emerson recorded a case of rupture of the deep epigastric artery caused by muscular strain. Schumann, in 1919, wrote a paper entitled, "Rupture of the Deep Epigastric Artery as a Clinical Entity". Behan, in 1920, reported a case of rupture of the rectus abdominis muscle. In 1922 Perman wrote a comprehensive article on hematoma in the sheath of the rectus abdominis muscle. In *Arch. f. klin. Chir.*, 1923, CXXII, S. 649, Wohlgemuth collected the cases of subacute rupture of the rectus muscle and of rupture of the epigastric artery. In the *Journal of the American Medical Association*, 1925, is a most interesting article by Carey Culbertson, entitled, "Hematoma Occurring Spontaneously in Sheath of Rectus Abdominis Muscle; Consideration of its Gynecological and Obstetric Significance; Report of Two Cases." This article of Culbertson's is a most satisfactory one. Those wishing to study in full the cases recorded by him can find them in the *Transactions of the American Gynecological Society*, 1925, Vol. 50, p. 124.

In this paper I shall report briefly five cases of hemorrhage into or beneath the rectus muscle occurring in Baltimore. Two of the five patients came under my immediate care, one was seen by Dr. Ralph W. Jack in the Obstetrical Out-Patient Department of The Johns

Hopkins Hospital, one was seen by Dr. Zachariah Morgan and operated upon by the late Dr. Maurice Lazenby at the Church Home and Infirmary, and one was observed in the Maternity Service of Dr. L. H. Douglass at the University of Maryland Hospital and operated upon by Dr. C. R. Edwards. After presenting these I shall refer to the more important recorded cases without attempting to review fully the literature on the subject.

BALTIMORE CASES OF HEMORRHAGE INTO OR BENEATH THE RECTUS

Case 1. Hematoma of the Abdominal Wall in a Patient Suffering from Severe Cardiac Disease and Gallstones

On January 10, 1903, in consultation with Dr. Thomas Linthicum, I saw a middle-aged woman who had severe cardiac disease, which had been associated with dropsy. She also gave a characteristic history of gallstones. In April, 1902, she had had erysipelas which had lasted four weeks, and shortly afterward had had swelling of the wrists and noticed abdominal enlargement. Two weeks later jaundice developed, which lasted three or four weeks. About this time cardiac symptoms were noted. Later on she was seized with a violent pain in the left leg, which lasted several hours and then extended to the right leg, reaching from the hip to the toes. Dr. Wells said that the circulation had stopped in the leg.

When Dr. J. M. T. Finney saw her a few days later, pulsation was again perceptible in the leg, but he agreed with Dr. Wells that the trouble was in the arterial circulation. The patient was ill for weeks, and when she was able to sit up, the limbs became markedly swollen.

After circulation had stopped in the leg, black spots, evidently subcutaneous hemorrhages, developed. These were noted from time to time, but were most marked in December. They varied in size from that of a cent to that of two hands. On December 15, 1902, she was seized with a severe pain, which seemed to be in the region of the liver, and on December 18, she was thought to be dying. A gradual improvement followed, until she was admitted to the hospital for operation.

When I saw her, there was, just above and to the right of the umbilicus, a deep-seated and apparently cystic mass, fully 16 cm. in diameter.

On January 15, the patient was removed to Baltimore. She stood the journey poorly, but under ether the pulse became more regular.

An incision was made to the outer side of the right rectus, directly over the center of the cystic mass. The swelling was due to a large hematoma between the transversalis fascia and the peritoneum. The cavity was irregularly circular, and had numerous little bays running off in all directions. The walls and the floor of the sac were thickened, and consisted of granulation tissue. The cavity was filled with dark, clotted blood. I packed this cavity loosely with gauze.

An incision was then made to the left of the median line, and curved upward to

the right. After the gallbladder adhesions had been separated, two gallstones, each about 5 mm. in diameter, were removed and the gallbladder was drained.

The hematoma cavity rapidly granulated and closed completely. The gallbladder wound also closed, and the patient was discharged in relatively good condition.

The symptoms have been given somewhat fully in order that the reader may see that the cardiovascular system was in such a condition that rupture of a blood vessel was much more prone to occur than in a healthy individual. This hematoma had undoubtedly been due to rupture of either an artery or a vein.

This patient is referred to in my *Diseases of the Umbilicus*, page 113.

Case 2. Hematoma of the Rectus Simulating a Hernia

Mrs. J. G. C., aged 67, was referred to me by Dr. E. M. Duncan, and admitted to the Church Home and Infirmary on January 4, 1933.

In 1930, she had undergone a cholecystectomy. During the year 1932 she had complained of dizzy spells and frequently of a feeling of faintness, and during the last six months she had had dyspnoea, especially upon exertion.

For a week prior to admission to the hospital, the patient had had a little tenderness and some discoloration over the left lower abdomen.

Examination of the chest revealed a pleural friction rub over the lower part of the right lung. The heart was somewhat enlarged and there was a distinct systolic murmur heard at the apex. There was oedema of the feet and ankles. The blood pressure was 232 systolic and 76 diastolic. The hemoglobin was 70 per cent. The Wassermann was negative.

Occupying the left lower abdomen was a somewhat lobulated tumor, 10 by 12 cm. The skin over this was dark bluish-black in color.

The tentative diagnosis was ventral hernia with hemorrhage; hypertension with moderate cardiac enlargement.

Operation, January 12, 1933. We made an elliptical incision beginning far over to the left and extending far over to the right. The upper arm of this incision began just below the umbilicus and its lower arm came within 4 cm. of the symphysis. The skin and fat were peeled away and where the bluish area was noted on the left side, we found oedema and a browning of the fat. With the fascia of the abdominal wall now well exposed, one could see a mass 9 by 8 cm. to the left of the midline and occupying a large portion of the space between the symphysis and the umbilicus. We cut the fascia and there was an immediate escape of tarry, clotted blood. There had evidently been a hemorrhage between the rectus muscle and its sheath. We removed at least 500 cc. of clots and a few that were organizing were left attached to the outer side of the sac. Two drains were put in the sac and brought out at the dependent portion of the incision, and the remainder of the sac was then overlapped with mattress sutures of chromic catgut. The layers of the abdominal wall external to the fascia were brought together with silver wire and silkworm gut. The patient stood the operation perfectly and was discharged on February 3, 1933.

January 7, 1935, Dr. Duncan told me that for the past three months the patient has been very uncomfortable as a result of her hypertension and her cardiac condition. On May 12, 1937 he informed me that the patient had died of her cardiac condition and nephritis, about one year previously.

Case 3. Rupture of the Right Rectus Following Diving Into Shallow Water: Chronic Appendicitis

This case, reported by Dr. Zachariah Morgan before the Gastro-enterological Society of the University of Maryland about three years ago, has never been published. Dr. Morgan kindly placed the data at my disposal.

Mr. R. R., aged 29, had had pains now and then in the right lower abdominal quadrant for several years; they never, however, had necessitated his going to bed. His last attack had occurred on July 23, 1927. The next day the patient was swimming and jumped off a raft. As the water was shallow, he went in flat on his abdomen. This caused severe abdominal pain and he had difficulty in getting out of the water. Later he felt relatively well except that his right lower abdomen was very sore. There was no nausea or vomiting. On the following day, July 25, he went to work but could not "carry on." Dr. Morgan had him admitted to the Church Home and Infirmary.

The abdomen was extremely tender over the right lower quadrant but there was no rigidity or spasticity. The soreness was so severe that he could hardly allow any one to touch him. On rectal examination there was no tenderness. The urine was normal; the leucocyte count 9,500. A diagnosis of acute appendicitis, with possible stone in the right ureter, was made.

Operation, by Dr. Maurice Lazenby. A right McBurney incision was made extending somewhat toward the median line. The right rectus was found to be filled with blood at this point and some of its fibers had been ruptured. The bleeding points were ligated. The peritoneum was then opened and a retrocecal appendix removed. Microscopic examination of the appendix showed a chronic inflammation.

The patient made a satisfactory recovery.

Case 4. Hematoma of the Abdominal Wall During Pregnancy

This patient was seen by Dr. Ralph W. Jack on the Outside Obstetrical Service of the Johns Hopkins Hospital in 1931. Dr. Jack's report of the case is as follows:

"She was a colored woman in her early thirties. She was about 7 to 7½ months pregnant. She was complaining of acute, severe pain in the abdomen. She had been wakened from her sleep by a sudden, sharp and severe pain which continued, with no relief. There was no history of any previous strain or injury. The temperature and respiration were normal; the pulse was slightly elevated. Palpation of the abdomen revealed exquisite tenderness and some muscle spasm in the right lower quadrant. A little above McBurney's point was a firm, tender mass, fixed in position and about 5 by 3 cm. in diameter.

"I was puzzled for a diagnosis and finally brought the patient to the hospital

for observation and to have her seen by the older members of the staff. There was some difference of opinion; most thought that the mass was the right ovary which had become strangulated. The diagnosis was not definite until Dr. Hofbauer saw the patient and diagnosed hematoma of the abdominal wall due to spontaneous hemorrhage.

"The patient was given palliative treatment. The symptoms rapidly disappeared, the hematoma softened and absorbed within a comparatively short time. She had no further trouble during the remainder of her pregnancy which terminated in a spontaneous delivery at term."

Case 5. Rupture of the Left Rectus Muscle in a Patient Twenty-Four Weeks Pregnant

Under date of January 25, 1935, I received the following letter from Dr. Charles Reid Edwards:

"I am enclosing an abstract of a case of ruptured left rectus muscle associated with hematoma within sheath of muscle, which came into the University Hospital on December 29, 1934, and was discharged on January 19, 1935."

This patient was operated upon by Dr. Edwards.

"M. F., colored, para 7, aged 32, twenty-four weeks pregnant, was admitted to maternity on Dr. L. H. Douglass' service, from the University Out-Patient Department, on December 29, 1934. Health during pregnancy had been very good until December 21, 1934, when she developed a bad cold associated with a severe cough. Two or three days before admission, patient coughed very hard and said that she felt like something was tearing in the left upper quadrant but she paid no attention to it. Early in the morning of the day of admission the patient had a severe coughing spell and said again she felt like something was tearing. One hour later she noticed a lump in the left upper quadrant which gradually increased in size, and she had considerable pain over this lump. She was seen by a medical student on the Outside Obstetrical Service who mapped out the lump and had her sent into the hospital. The lump had doubled in size by the time she arrived at the hospital, and when I saw her soon thereafter the mass followed the course of the left rectus muscle and had increased very materially in size after her admission to the hospital. The mass was firm, painful on pressure, and extended from the ensiform and costal cartilages on the left side almost to the symphysis pubis, and apparently was confined to the sheath of the left rectus muscle. My impression was that she had a hematoma in the sheath of the muscle and I advised immediate operation.

"I explored the sheath of the left rectus muscle under novocaine infiltration anesthesia and found a rupture of the muscle at the upper tendinous insertion; rupture involved about one-third of the transverse measurement of the muscle. After expressing a large blood clot which measured about 500 cc., and mopping out the wound, I found an artery at the site of rupture, which was pumping vigorously. The vessel was ligated, muscle repaired with No. 1 plain catgut and the wound closed. The patient made an uneventful recovery."

THE SYMPTOMS OF HEMATOMA OF THE RECTUS MUSCLE

A study of the reported cases shows that some of the patients had met with a direct injury causing rupture of the muscle; in other cases there was an indirect injury with the development of hemorrhage into the rectus. Occasionally the bleeding into the muscle occurred during pregnancy; more frequently the symptoms were noted in patients who were suffering from some debilitating disease and in whom the slightest exertion might be followed by rupture of one rectus muscle.

Cases of direct injury of the rectus muscle are fully considered by Maydl and Wohlgemuth, and their diagnosis is so clear that they need not be considered here.

The symptoms of hematoma of the rectus, due to indirect injury, are very acute. The hemorrhage may be due to rupture of the muscle, or to tearing of the deep epigastric artery, or to the simultaneous injury of both structures. The hemorrhage usually occurs below the umbilicus and is nearly always limited to one side. In a few cases the bleeding has been above the umbilicus. According to Wohlgemuth's tabulation, it was noted 45 times on the right side, 33 times on the left side, and in only 5 cases above the umbilicus. The swelling at the point of the hemorrhage has been described as the size of an egg, the size of a doubled fist, as large as a child's head, and in Ehrenfest's case it was as large as a football. Sometimes there has been a vague history of slipping, or the patient has turned over suddenly, or an acute pain has immediately followed coughing. Occasionally there is discoloration of the abdominal skin. It was noted in von Renner's, Hartmann's, Blond's, Perman's cases 2 and 9, in Fothergill's, Halperin's, and in Stoeckel's case 2.

As already clearly shown in Max Brödel's plates, the lower part of the rectus has little or no sheath posteriorly; thus, when the hemorrhage is below the umbilicus, the free blood may lie directly against the peritoneum, producing an irritation causing severe pain and immediately suggesting an acute intra-abdominal lesion.

A short report of some of the individual cases will give the reader a clear idea of the various symptoms noted.

Von Renner's patient was a woman aged 63, who had never been pregnant. She had suffered a slight hemiplegia two years previously. Without apparent

cause, she was suddenly seized with severe pain in the right lower abdomen and was compelled to remain in bed. There was no vomiting and no dyspnoea. The skin below the umbilicus was stained a light blue. Two physicians regarded her condition as due to some intra-abdominal lesion. In the right lower quadrant, a resistant area, the size of one's hand, was palpable, but no mass was evident vaginally. At operation, the interior of the abdomen was found to be negative

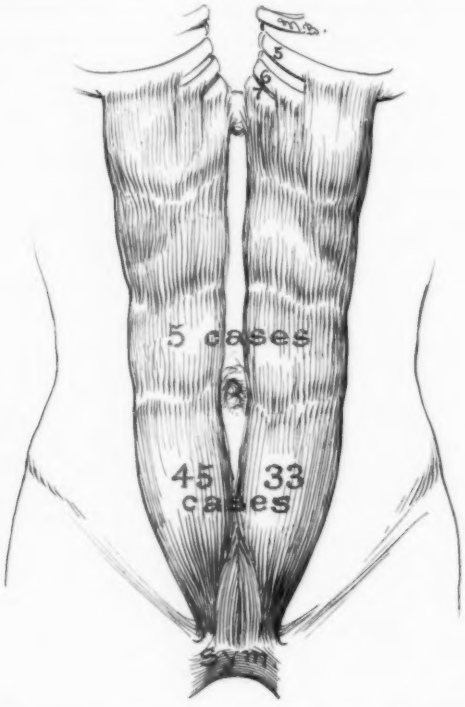

FIG. 10. Distribution of cases of hemorrhage into or beneath the rectus as given in Wohlgemuth's paper.

except for ecchymosis of the peritoneum extending into the broad ligament. A hematoma was found beneath the right rectus, with separation and laceration of its fibers, and with discoloration of the subcutaneous tissue.

Hartmann's first case was that of a healthy man, 42 years old. On the 12th of February, 1914, during an attack of coughing, he felt a sharp pain in the left groin accompanied by a tearing sensation. Almost immediately there appeared a

small swelling in the lower part of the left hypogastrium. When Hartmann saw him, the patient had, on the left side, on a level with the lower part of the rectus sheath, a hard swelling, very painful, which presented all the characteristics of a tumor situated in the muscle, a tumor that did not disappear during contraction of the muscle, as is customary with intra-abdominal tumors, but one that remained fixed during muscular contraction, as does not occur with tumors situated in front of the muscles. Over the tumor there was slight ecchymosis of the skin. This patient showed all the signs of a hematoma following rupture of the rectus muscle.

Blond, in 1924, reported the case of an obese woman, aged 73, who had had 14 pregnancies, 7 going to term. For several years she had had difficulty in breathing when walking and climbing. For six weeks she had had coughing and for three weeks this had caused distress beneath the edge of the ribs on the left. She had a bronchitis. About two months before admission to the hospital, the patient noticed a bluish discoloration on the upper right arm. This was painful. There was no fever; no history of injury. In two weeks the pain and discoloration had disappeared. Two weeks before admission there appeared a similar discoloration of the dependent portions of the abdominal folds. There was no history of injury. Examination showed an indefinite, fluctuant, tender swelling the size of a child's head, in the upper left quadrant. The skin below the tumor was bluish red and at several points confluent petechiae were noted. Aspiration brought fluid blood. At operation old clots, organized blood and fluid blood were found in the upper rectus sheath, with laceration of some muscle fibers.

Perman's case 2 was in an agricultural laborer, aged 34. When lifting a heavy sack, he experienced cutting pains in the left side of the abdomen. He was better the next day. Later he fell down backwards and had a sharp pain at the same spot. On the following day, he noticed a hard resistant area to the left of the navel. The pain was now constant. On admission, a tumor the size of a child's head was seen to the left of the navel. Some days after admission to the hospital, the skin around the navel showed a yellowish-green discoloration, over an area the size of a two-crown piece. There was also discoloration along the linea alba from the umbilicus to the symphysis. On puncture, dark blood was obtained. At operation a hematoma was found; also partial rupture of the left rectus muscle.

Perman's case 9 was in a barber aged 47. For the previous three weeks he had had a bad cold and cough but had attended to his work. During an attack of coughing, he had a slight pain in the right side of the abdomen. The pain suddenly increased in intensity and he was obliged to go to bed. On admission to the hospital, a painful resistance, a hand's breadth in length, could be made out in the right abdomen. Its medial margin was located two fingers' breadth from the median line. Over the resistant area there was a bluish discoloration of the skin. Hemorrhage of the rectus was diagnosed. On puncture, about half a pint of old blood was evacuated from the resistant area.

Fothergill's patient was a woman of 57 who had been quite well until she had severe abdominal pain. There was considerable swelling in the right lower abdomen. Two days later diffuse black bruises appeared on the surface of the

lower abdomen over an area 8 by 4 inches. There were many patches of subcutaneous hemorrhage. On abdominal examination, the physical signs suggested the presence of a fibroid tumor. On pelvic examination an ovarian cyst seemed probable. When the patient was asked to sit up, thus bringing the recti into contraction, the swelling above the symphysis could still be felt and became quite fixed. This indicated that the tumor, felt externally, was really in the abdominal wall. The diagnosis was now changed to hematoma of the abdominal wall with a co-existing ovarian cyst. This diagnosis was correct. The patient was operated on and made a satisfactory recovery.

Halperin, in 1928, reported the case of a woman, aged 71, whose general health had been good apart from an occasional attack suggesting gallstones. Suddenly, while turning over in bed, she had a stabbing pain in the right upper abdomen, followed by nausea, vomiting, sweating and partial collapse. Examination two hours later revealed a tender, hard mass extending from the gallbladder area to a point slightly below the level of the umbilicus. The mass was 3 inches in diameter; respiration 22; pulse 80. Two days later, ecchymosis appeared in the skin around the umbilicus and over the right abdominal wall. At operation, a hematoma was found beneath the upper portion of the right rectus. The abdomen was not opened.

While in all of the cases just mentioned there was some ecchymosis in the abdominal wall, this sign is relatively rare. In 1919, I drew attention to the fact that in some cases of extra-uterine pregnancy there is a bluish appearance of the umbilicus, and in a few cases a play of colors in this region suggesting a black eye. In the cases of hematoma just cited, pregnancy was naturally out of the question. The patients were usually women beyond the menopause or were men, and the hemorrhage came from the abdominal wall and not from the abdominal cavity.

DIFFERENTIAL DIAGNOSIS

Hematoma of the rectus muscle has simulated nearly every form of acute abdominal lesion. When it is situated in the right lower abdomen the case may be diagnosed as one of acute appendicitis, ovarian cyst with a twisted pedicle, ovarian abscess, ruptured tubal pregnancy, or possibly intestinal obstruction. When rupture has occurred low down in the left rectus the lesion has been taken for an abdominal hernia or for a marked thickening of the sigmoid. Where the rupture of the rectus has occurred above the umbilicus, hydronephrosis or acute gallbladder disease has been diagnosed.

In many cases the true condition has remained obscure until an incision has been made. In cases in which rupture of the rectus sheath had occurred, staining of the abdominal fat was noticed the minute the skin was cut. Where the rectus sheath was intact, only on incising the sheath was the true nature of the condition recognized in the obscure cases.

A survey of the following cases will enable the reader to see clearly how difficult the diagnosis may be unless he is on the lookout for hematoma of the rectus.

Hartmann's patient, a woman of 56, was admitted to the hospital as an emergency case with the diagnosis of appendicitis. At the end of December 1916 she had had grip, followed, in January 1917, by pulmonary congestion with frequent cough. She said that on the 13th of February, in the midst of an attack of coughing, she had felt a sharp tearing in the right side of the abdomen. (Hartmann says: "We did not pay sufficient attention to this part of the history.") The stomach was distended and painful, there was vomiting, retention of urine, obstruction of the bowel and no passage of gas. On the right side of the abdomen, one could feel, below and to the right of the umbilicus, a diffuse area of thickening with muscular rigidity, which extended to the iliac fossa. This coincided very well with the diagnosis of appendicitis made by the physician who had sent her to the hospital. Hartmann remarks: "I should say that, from February 16, on palpation I got the sensation of a tumor in the midst of the general puffiness of the region." On February 24, the retention of urine had ceased, the bowels were regular, the distention of the abdomen had disappeared and one could feel in the middle of the right hypogastrium a generally rounded mass, which appeared to be limited, painful on pressure and giving the impression of deep resistance. Uncertainty was gone and one could feel a tumor. Hartmann continues: "I thought then of an ovarian cyst with a twisted pedicle and the possibility of peritonitis. However, on vaginal examination no tumor could be demonstrated.

"On the 8th of March I made an abdominal incision in the median line. As soon as the abdomen was opened, I could see that there was no peritonitis nor the least trace of inflammation. I then raised the right flap of the abdominal wall and from the general appearance I could see that the peritoneum was very slightly arched and presented a brownish tint. It was only then that I had the idea of a subperitoneal hematoma following partial rupture of the muscle.

"Closing the median incision, I made a transverse incision outside. The subcutaneous tissue was absolutely normal; the anterior surface of the sheath of the rectus muscle, as well as that of the muscle itself, was also normal. Only toward the outer edge of the muscle could I see oozing of a serous, bloody, brownish fluid, and was thus able to prove the existence of a true hematoma of the muscle. It was the influence of a hematoma with rupture of the deep part of the rectus muscle

that brought about the reflex phenomena of the peritoneal syndrome that this patient presented on her arrival."

Emerson's patient was a woman of 42. She had had four children and seven miscarriages. Her Wassermann was negative. She jumped from the floor in order to adjust a curtain rod. Sudden and severe pain developed in the lower left abdomen. The pain was so severe that she fainted. The shock and collapse necessitated stimulation. She looked very pale and was nauseated. A diffuse, tender and painful swelling gradually appeared in the left lower quadrant, becoming definite in eight days. A tentative diagnosis of abdominal hernia was made. Operation disclosed about two cupfuls of clotted blood between the left rectus and the peritoneum. The blood had accumulated about the severed ends of the deep epigastric artery.

Perman's case 7, a corpulent woman of 52, the mother of seven children, developed a cough and went to bed because of a sudden aching pain in the left lower abdomen. This was accompanied by a stinging sensation. The pain increased in severity during the following week. Examination showed râles in the lungs, a plum-sized umbilical hernia, not occasioning symptoms, and a painful resistance in the left lower abdomen. There was no discoloration of the skin. On vaginal examination, a movable painful swelling, the size of a doubled fist, apparently cystic, was made out to the left of the uterus. The diagnosis was strangulated ovarian cyst. Operation was undertaken for the care of the hernia, and an abdominal exploration was made. The sheath of the left rectus was blue-green in color and contained much blood. The pelvic organs were normal. The peritoneum was blood-stained but smooth and shiny.

Wohlgemuth's patient was a 62-year-old, very fat woman, who, after severe coughing, was seized with a sudden pain in the right lower abdomen. The patient had no stool and passed no gas. On examination there was marked distention of the right lower abdomen and a tumor, larger than a fist, could be palpated in that region. This tumor was painful. A tentative diagnosis of an ovarian cyst with twisted pedicle, or appendicitis, was made. There was a hematoma of the right rectus accompanied by tearing of the rectus muscle. There was no ovarian cyst.

Culbertson's case. A well developed woman of 34, while driving from a tee in a game of golf, experienced sudden, sharp pain in the right lower abdomen. Five days later she played golf again and while taking her shower-bath after the game, she noticed a swelling in the right side, and because of this and the pain she sent for her physician. That evening she attended a dinner party, later driving twenty-five miles by motor. After she arrived, she partially collapsed. During the next five days she suffered from chills on two different nights. When she entered the hospital on the seventh day the diagnosis was 'strangulated ovarian cyst or tubal pregnancy.' Her menstruation had, however, been perfectly normal. "Upon examination, the abdomen was flat, firm, soft and elastic, except for a somewhat indefinite mass or resistant area just above Poupart's ligament on the right. This area was tender and painful. The uterus lay in retroversion, was

normal in size and freely movable. The left appendages were prolapsed, but on the right side a fixed, tender mass, the size of an orange, was palpable. The most notable thing about this mass was that it appeared to lie in the anterior pelvis, as if anterior to the round ligament, or, as described in the case record, behind Poupart's ligament."

Operation. "The skin of the abdominal wall showed no discoloration, but as soon as the subcutaneous fat was reached, an extensive ecchymosis was evident, involving the fat, aponeurosis, and the right rectus muscle. The structures were not only discolored, but also infiltrated and swollen, and between the lower portion of the muscle and its deep fascial sheath, lay several ounces of clotted blood. This was removed and revealed the muscle fibers not divided sharply, but as if shredded, and there was some separation of the muscle bundles longitudinally. This area, as it involved the muscle, extended from the symphysis for 10 cm. upward. There was no active bleeding. The ecchymosis involved the peritoneum which, though markedly discolored, was smooth and shiny on its inner surface, and extended farther into the right round and broad ligaments. This discoloration was apparent throughout the right pelvic wall as far down as the utero-sacral ligament, but stopped short of the tube, ovary and uterus by a sharp line of demarcation. The uterus and appendages were normal."

Morris Flexner's patient was a female, aged 28, seen on June 16, 1931. During the course of a golf game that afternoon she had noticed a sharp pain in her lower right abdomen two or three times. This had lasted only a few minutes. In the lower right abdomen was a definite resistance and a small mass, 1.5 by 2 inches, was felt. It was somewhat tender and could be easily displaced in all directions. Dr. Flexner at that time thought he was dealing with a small inflammatory mass about the appendix. Dr. Wallace Frank saw her that evening, did not think the mass was an appendix and advised watching. Dr. Flexner saw the patient again on June 24. That afternoon, while playing golf, she had had sharp pain in the same region and also a feeling of faintness. At that time a definite mass, 3 by 4 inches in diameter, could be found in the right lower abdomen. It was somewhat movable. Next morning an operation was performed. It was noted that there was some blood just beneath the fascia and further investigation showed a hematoma in the right rectus muscle.

Ehrenfest, in a personal communication to Wohlgemuth, reported the case of a woman who had been coughing for three days. A swelling, the size of a football, developed in the right lower abdomen. It was accompanied by severe pain and tenderness. A diagnosis of ovarian tumor was made. Operation revealed a massive hematoma in the right rectus sheath. There was also tearing of the muscle.

Culbertson in his monograph included a case of Carl Beck's. The patient, an obese woman of 40, who had had six children, was suffering from a severe bronchitis. She had had a cough for several days and had begun to feel pain in the right upper quadrant of the abdomen. Examination showed a hard, tender swelling, the size of a hen's egg, in that region. Vomiting, jaundice and con-

stipation were absent. A diagnosis of gallbladder disease was made. Operation revealed that the mass was a hematoma in the sheath of the rectus muscle just beneath the free edge of the ribs. There was some laceration of muscle fibers but no active bleeding. The peritoneum was not opened.

Hilgenreiner's patient was a woman, 56 years old, with marked development of fat and with arteriosclerosis. At the end of 1922 she had grip with severe coughing. On the 6th of January, 1923, she suddenly developed severe pain in the lower abdomen. This became almost unbearable. There was peritoneal irritation. In the right lower abdomen was a tumor the size of a child's head, very sensitive. A tentative diagnosis of ovarian cyst, with a twisted pedicle, was made. On making an abdominal incision, the right rectus sheath was found to contain a large cavity filled with blood clots. In the anterior surface of the rectus, a short distance below the umbilicus, was a tear in the muscle.

Kuhle reported the case of a woman 42 years of age. The day before admission to the hospital, in the evening, she was suddenly seized with pain in the right lower abdomen. There was no history of injury. The patient was well nourished, had a great deal of fat in the abdominal wall and consequent sagging. There was great abdominal pain, particularly in the right lower portion. Occupying this area, was a very painful, firm, elastic, immovable tumor, the size of a fist. Pelvic examination was not satisfactory. The diagnosis was appendicitis, abscess, or ovarian cyst with a twisted pedicle.

The next morning an abdominal section was made. On making the incision, a bluish-red color was noted in the anterior rectal sheath. On opening the sheath a large hematoma was found in the rectus. It consisted of clotted blood; there was no fresh blood. The rectus itself was markedly hemorrhagic. No bleeding vessel was detected. On opening the abdomen, the bluish appearance of the hematoma was clearly visible on the peritoneal side. The appendix was adherent. The pelvic structures were normal. After closing the abdomen, the hematoma was dissected out. Healing followed and the patient was discharged in three weeks.

CAUSES OF HEMORRHAGE INTO OR BENEATH THE RECTUS ABDOMINIS MUSCLE

1. Muscular Exertion

Rupture of the rectus abdominis muscle now and then occurs in the athlete who, as a result of his contortions, has put a quick and unusual strain on the muscle.

Koerte treated an obese woman who, while undressing, had some difficulty in removing an under-garment. A sudden pain was felt in the right upper abdomen and a swelling soon appeared in this region. There was tenderness with rigidity. A diagnosis of probable

cholelithiasis was made. At operation, a hematoma of the right rectus was found.

Wiener's patient was a woman of 42. She had slipped on the floor six weeks before coming under observation. Later she had had a slight pain in the right lower abdomen and a swelling had developed there. On examination, a firm, elastic, non-tender mass could be felt. This was slightly movable. A diagnosis of desmoid tumor was made. At operation a hematoma of the right rectus was found.

As mentioned at the beginning of this article, Richardson's patient was a man of 25. When leaping, he developed a rupture of the right rectus. He was operated upon and recovered.

Rupture of the rectus has occurred when the patient was in a recumbent position and attempted to rise suddenly.

A careful study of the cases reported clearly indicates that in many instances the patients were suffering from some debilitating or infectious disease.

2. Pregnancy

Rupture of the rectus muscle is occasionally noted during pregnancy. Two of the five cases of hemorrhage into the rectus that I am recording occurred during pregnancy.

A consideration of some of the reported cases may be of interest.

Stoeckel says: "I know of no observation where hematoma of the abdominal wall has occurred in the course of pregnancy where there has been no apparent external cause. I accordingly want to report two cases of this character."

Stoeckel's case 1, the mother of four children, during the two years preceding her admission, had aborted twice, once at the third and once at the fourth month. On admission to the hospital, on March 26, 1900, she said that she was six months pregnant, and that she had been noticing movements of the child for about three weeks. As a result of a cold, the patient had recently been coughing severely. During one of these coughing spells, about two weeks before admission, she had suddenly been seized with severe pain in the right lower abdomen and had noticed a swelling just above the right groin. The pain had diminished during the next few days. There was no hemorrhage from the vagina. On the morning of her admission, there was a sudden and abundant escape of water.

On admission, the most striking thing noted was the condition of the abdominal wall. Directly above the symphysis, more prominent on the right, was a large swelling which reached almost to the umbilicus. The proof that the tumor lay in the abdominal wall was easily determined. One could grasp it between the

fingers. The patient was delivered the same night. The size of the tumor diminished during the patient's sojourn in the hospital. At operation, the right rectus sheath was split and a hematoma found. The cavity was emptied, curetted, and the patient made a good recovery.

Stoeckel's case 2 had had five normal labors and, nearly two years before admission, a spontaneous abortion. Fourteen days before she entered the clinic, she had been delivered of her sixth child, the labor being normal. She said that eight days before the last labor, during violent coughing, suddenly in the right lower abdomen something tore and immediately thereafter she noticed a small tumor which, each time she coughed, became larger and which was very painful when she moved. During the labor the midwife diagnosed twins. The tumor on the right side was supposed to be the head of the second child. The patient was delivered spontaneously of a living child. The placenta soon followed. The hemorrhage was small in amount. Following labor the temperature was normal; the swelling in the right lower abdomen remained unchanged but appeared to have become a little smaller in the last few days.

On examination, a tumor was found in the right hypochondrium. It was about the size of a child's head. It began about a finger's breadth below the edge of the ribs on the right and extended as far as the navel. It was sharply circumscribed, was uniform, elastic and fluctuated. It seemed to be free from the overlying skin. It could be moved to and fro with the abdominal wall. On the left side, below the tumor, and between the umbilicus and symphysis, the skin and subcutaneous connective tissue had a diffuse, greenish-brown color, due to imbibition of blood. The extensor sides of the upper and lower extremities, and, to a lesser extent, the front of the thorax, showed numerous, miliary, bright red petechiae scattered irregularly over them. These were the size of pin-heads. The diagnosis was 'multiple hemorrhages of the skin, large subcutaneous hematoma in the right hypochrondrium.'

Operation. On making an incision, about two handfuls of partly fluid, partly coagulated, brownish-black blood were removed. The hematoma lay in the sheath of the right rectus, the muscle bundles of which were partly torn. The cavity was drained.

The petechiae disappeared, and the wound healed.

Stoeckel says that, in case 1, the situation of the hematoma corresponded with the region of the right inferior epigastric artery; in case 2, the situation of the clot was somewhat higher and it probably originated from the right superior epigastric artery.

Vogt, in 1913, after referring to Stoeckel's two cases, reported one of his own. In the beginning of December, a woman 21 years of age, who had had two children and who had previously been well, entered the clinic for delivery. She was examined every three days externally. Nothing abnormal was found apart from the very movable position of the child.

On January 3, at 8 P.M., pains commenced. They occurred about every three minutes and were regular. On January 4, at 1:40 A.M., spontaneous labor

took place. The afterbirth came away ten minutes later. Several hours after delivery, the patient complained of severe pain directly above the symphysis. On investigation, the uterus was found to reach as high as the umbilicus; it was well contracted and only slightly sensitive. Above the symphysis were two characteristic, superficial tumors, over which the skin and also the fascia could be slid. On careful examination, with the patient lying down and also when sitting, it was demonstrated that there was a symmetrical swelling of the lower end of both recti muscles. These tumors were separated from one another by the linea alba which measured three finger-breadths. Despite rest in bed and the application of an ice bag, the tumors increased in size up to the third day, although the pain became less. She was discharged on the 21st day. The swelling had diminished but was still perfectly visible on both sides.

Examination four weeks after the patient went home failed to reveal any trouble above the symphysis. There was a broad diastasis of the muscles.

Vogt says: "In our case the hematoma must have occurred during labor. Stoeckel's two cases were cured by drainage after incision. The course of our case teaches us that a large hematoma will disappear in a short time by conservative treatment and without operation."

Andrews says: "In the *Medical Review* for March 1916, p. 114, there is the abstract of a case which was recorded by E. Toft (*Hospitalstidende*, September 15, 1915, p. 933).

"A pregnant woman, who had a troublesome cough, suffered from very severe pain in the right side of the abdomen when she was six months pregnant. To the right of the uterus, a slightly movable tumor, 12 cm. long, 6 cm. wide, and 2 cm. thick, was found. This was very tender and difficult to separate from the uterus.

"An intraperitoneal tumor, probably a placental hematoma, was diagnosed. An incision was made over the external border of the right rectus. The subcutaneous tissues were found to be infiltrated with blood. As the incision was deepened, a large cavity, filled with very firm clots of blood, was opened. The cavity was from 15 to 20 cm. long, bounded behind by the somewhat thickened fascia transversalis. *In the upper part of the cavity was a small opening through which blood had escaped into the peritoneal cavity.*"

Andrews' own case 1 was most instructive. The patient was a woman, aged 39, who had been well previously except for acute rheumatism in adolescence. The illness occasioning the report occurred while she was suffering from a severe cough and when she was propped up in bed. There was sudden pain in the right lower quadrant of the abdomen. It became increasingly severe.

The patient thought she was about eight months pregnant and had noticed no abdominal enlargement disproportionate with the duration of gestation. She was anemic and looked very ill. Temperature 101°, pulse 135, respirations 28 to 36. Cough and dyspnoea were severe and the urine contained albumin and casts. "The abdomen was filled by a large swelling which bulged into the right flank. A deep sulcus could be felt at the upper pole of the swelling, dividing a larger part on the right side from a smaller on the left side, which was evidently the

uterus, as contractions could be felt in it." The diagnosis of hydronephrosis was made.

Thirty hours after admission, a premature labor took place. The diagnosis was then changed to inflammatory ovarian cyst, and a week later, when the patient's condition had improved, operation was undertaken. The tissues beneath the skin were ecchymotic and the swelling was found to be entirely in the abdominal wall, representing old blood clots, filling a large space behind the rectus and *extending up almost as far as the ribs*. There were nearly two pounds of blood.

In a personal communication dated Sydney, Australia, March 14, 1911, Dr. Fiaschi tells me that his father had a very interesting case just before Christmas 1910. A young woman developed a hematoma of the left rectus above the umbilicus during or just after labor. She came from the country, and Dr. Fiaschi and his father had thought prior to operation that they might find a ruptured or suppurating hydatid of the abdominal wall or of the left lobe of the liver.

Lantuéjoul and Bernard-Griffiths, in 1933, reported an interesting case of a woman who was seven months pregnant and had a rupture of the right rectus.

3. Typhoid Fever

Rudolph Virchow, in 1857, drew attention to rupture of the rectus muscle in typhoid fever and gave a fascinating description of the hyaline or waxy degeneration of the rectus abdominis muscle frequently occurring in this disease.

Zenker, in 1863, had the opportunity of making many autopsies on patients dying during a very extensive typhoid epidemic. He followed out in detail the degenerations occurring in the rectus abdominis and other muscles in patients suffering from this disease. His monographs on this subject were so thorough and explicit that the changes are known as *Zenker's degeneration*.

W. W. Keen of Philadelphia, in 1876, dealt with this degeneration fully in his Toner Lecture.

Hilgenreiner, in 1923, when considering hematomas of the abdominal wall in the aged, referred to the rôle played by typhoid fever. He says: "In abdominal typhus [typhoid] ruptures of the recti muscles are not rare. In 202 cases of typhoid, autopsied in the Charity Hospital, Berlin, rupture was noted 11 times." He further says: "Ruptures are also found in other severe diseases, miliary tuberculosis, recurrent fevers, smallpox, tetanus, burnings, frost-bites, trichinosis and icterus neonatorum."

From the foregoing, it is perfectly clear that changes in the rectus abdominis and other muscles are frequent in typhoid fever, and

that Zenker's degeneration is undoubtedly responsible for the hematomata of the rectus which occasionally develop in such cases. Typhoid fever is now, fortunately, in large measure under control; hence hematomata from this cause will, in the future, be rare.

M. Handfield-Jones, when discussing Andrews' cases at a meeting of the Obstetrical and Gynecological Section of the Royal Society of Medicine, reported the following very instructive case in which a patient who was pregnant, and who also had typhoid fever, developed a hematoma of the abdominal wall.

"The patient, a primipara, was admitted to the medical ward of St. Mary's Hospital suffering from an attack of typhoid fever. The pregnancy was advanced to the middle of the seventh month.

"About the third week of the fever, labor pains came on and a dead foetus was expelled. During the third stage pain was complained of in the region of the right rectus muscle about the level of the navel. It was noticed that a lump had formed here about the size of an egg and this slowly increased until, next day, it formed a tumor equal in size to a small cocoanut. The skin over the mass was of a bluish colour, and the tumor itself felt semi-solid in character. By degrees the lump slowly became smaller and at the end of six weeks had practically disappeared.

"As no operative interference was called for, the nature of this swelling could not be ascertained with certainty, but from its mode of onset and from its gradual absorption there can be little doubt that it was formed by an extravasation of blood into the tissues around the rectus muscle."

4. Influenza or Influenzal Pneumonia

The appalling epidemic of influenza of 1918–19 furnished ample opportunity to study degenerations occurring both in the heart muscle and in the muscles of various parts of the body. Cooper Cole, William G. MacCallum, Beals, Blanton and Eisendrath, Homer Gage, S. Burt Wolbach, and others, have studied extensively the changes in the rectus abdominis associated with influenza.

Cooper Cole, in his preliminary report of the influenza epidemic at Bramshott, in September–October, 1918, drew attention to the fact that even in mild cases in which the temperature became normal within from three to seven days, without disturbance of pulse or respiration, considerable weakness persisted and renal irritation was usually present. Even these mild cases showed a tendency to tachycardia on slight exertion during convalescence.

Cole further states:

"Myalgia and muscular weakness were very common symptoms. Abscesses were found in some muscles, and marked degeneration was repeatedly noted in the rectus abdominis. The muscle looked grey, cooked, and readily flaked, three hours after death. Often there was marked hemorrhage, as much as two ounces, into the sheath of the rectus, and the muscles themselves were frequently found spontaneously ruptured as cleanly as though cut with a knife. The hemorrhage was sometimes present throughout the length of the sheath from the costal cartilages to the pubis, though usually only in the lower quarter. Myocardial degeneration was frequently very obvious at section."

Dr. William G. MacCallum who had most unusual opportunities for studying influenza in the various United States Army camps during the epidemic, has written most extensively on the subject. He kindly furnished me with the following memorandum relative to the findings in the recti muscles:

"During the epidemics of pneumonia in army camps following measles and influenza, there was found in a number of cases a symmetrical rupture of the two sides of the rectus abdominis in its lower third. The separation of the torn ends was accompanied by a considerable hemorrhage such as is often seen in the same position in typhoid fever—the so-called Zenker's degeneration of the muscle. This is due to a hyaline degeneration of the fibers which are broken into irregular masses of glassy material with no trace of the former striation. The sarcolemma sheath collapses and before long such weakened muscles tear with coughing or some other strain and the hemorrhage occurs, but in some cases there was no tear and the hyaline change was found only upon microscopical examination. In other cases streptococci, pneumococci and other organisms were found to have localized themselves in the degenerated area and to have produced abscesses. It seems that the hyaline change is not the direct effect of local infection, but that it is caused by some toxic process after which the bacteria lodge in the necrotic material.

"No good explanation for the special localization of the injury in the lower third of the rectus abdominis has been offered. (In Monograph 10 of the Rockefeller Institute, April 1919, cases 45, 187, 192, 205 showed these changes. In the Johns Hopkins Hospital Reports, 1921, XX, Fasc. II, Cases 80, 82, 87, 88, 223, and 6142 present the same changes. We have had other cases in small numbers among the current autopsies 9121, 9157, 9193, 10077, 10266, 11039, 11212, 11833.)"

Beals, Blanton and Eisendrath in their report "Abdominal Complications of the Influenza Epidemic at Camp Custer, Michigan," emphasized the changes noted in the rectus muscle. These authors report the findings in 140 cases of bronchopneumonia following in-

fluenza and coming to autopsy in all stages of the disease. Their report is a most interesting one. Under the heading, "Rupture of the Rectus Muscle," they say:

"Rupture of the rectus muscle occurred with such frequency as to attract special notice. Eight cases showed this condition at necropsy. The rupture occurred regularly midway between the symphysis pubis and the umbilicus. It was never complete, usually involving only a few fibers, and was always bilateral. It was accompanied by hemorrhage under the sheath of the muscles. In one case this hemorrage was extensive, dissecting its way downward in front of the bladder. In another case a broken down hematoma under the muscle sheath showed hemolytic streptococci. In cases which have been studied microscopically the same condition was demonstrable, namely, polymorphonuclear leucoccytes, and mononuclear wandering cells accumulated diffusely between the muscle fibers, and here and there localized into definite abscesses. Poorly staining muscle fibers, sometimes broken and contracted, with quantities of erythrocytes free in the tissues, completed the picture. The presence of well preserved erythrocytes in the tissues points to the fact that rupture was usually a late occurrence in the disease. The probable explanation of these striking breaks of the rectus abdominis is that a localization of the infection in these muscles with abscess formation so weakens the muscle that rupture occurs with violent coughing or terminal muscle spasms. In three of the cases the cough had been so severe that a special notation of the fact was made on the daily record."

Ingraham, in discussing Culbertson's paper, says:

"There must have been many of these cases of hemorrhage in the rectus muscle occurring during the influenza epidemic in the army. Dr. J. N. Hall, of Denver, a consultant, visiting the different camps, told me that he had encountered several such cases following instances where there had been severe coughing. I, personally, had occasion to open the muscle in one such case, there being present a considerable mass at the lower end of the left rectus. A large hematoma was encountered. This I attributed to the tearing of the muscle and hemorrhage from a small vessel, though it is possible this bleeding may have arisen from the rupture of a large vessel, such as the epigastric."

Gage refers to the influenza observations of Wolbach. He says:

"In a series of autopsies performed during the influenza epidemic at Camp Devens by S. Burt Wolbach, lesions precisely similar to those described in typhoid were noted in nine cases. They ranged from a swollen, opaque, yellowish-white appearance to the presence of large masses of blood clot occupying considerable areas of the recti muscles."

The following extracts from Wolbach's autopsy reports show the extent of the observed lesions:

"Case I (September 30). H. N. R. Recti for 8 cm. above pubes are swollen and infiltrated with blood clot, and muscle is softer and more friable than normal.

"Case II (October 1). J. C. Recti from umbilicus to pubes swollen, and upper half of each is infiltrated with dark red blood clot. Fibres are widely separated and the cavities 0.5 to 1 cm. in diameter filled with clot. Pubic ends of muscles are pale, opaque and friable.

"Case III (October 3). E. G. Lower 8 cm. of recti opaque, pale, friable, yellow, and in the left small areas of hemorrhage 0.2 to 1.2 cm. long separating muscle fibres at junction of normal and yellow portions.

"Case IV (October 4). G. P. Lower 8 cm. both recti swollen, opaque, yellowish, white and friable.

"Case V (October 4). M. L. Muscles and chest normal except lower end left rectus is opaque, yellowish and slightly swollen for distance of 2 cm.

"Case VI (October 7). C. W. Upper part of recti streaked in pale grayish red lines, and on the right side are punctate hemorrhages.

"Case VII (October 8). F. LeC. Lower ends of both recti from umbilicus to pubes greatly distended with dark red blood clot, and the retroperitoneal tissue on each side is infiltrated with blood for a distance of several cm. Muscles on section are soft, paler than normal, with large masses of blood clot separating fibres longitudinally and occupying spaces between transverse tears of the fibres.

"Case VIII (October 11). A. H. Lower one-half rectus contains yellow opaque areas of striae; on section, portions of the muscle 1 to 2 cm. in length and 0.5 cm. in width are greenish yellow in color, opaque—small areas of hemorrhage in muscle substance. Similar conditions at upper and right rectus.

"Case IX (October 11). W. J. E. Recti at extreme ends pale reddish gray or pink; no hemorrhage."

In the microscopic study of sections removed at autopsy, Dr. Wolbach found similar, though less marked, changes in the other abdominal muscles and in other muscles of the trunk, such as the pectorals and the latissimus dorsi.

From these observations it seems quite clear that a Zenker's degeneration of the recti muscles is a not infrequent accompaniment of influenza and influenzal pneumonia, that the muscle fibers become so friable that rupture occurs with varying degrees of hemorrhage, and that more rarely still the blood clot may be infected by the predominant organism with resulting abscess.

R. I. Harris's case is a striking example of a patient with influenza developing a hematoma of the abdominal wall resembling in nearly every particular an acute appendicitis.

A widow, aged 28, had suffered for ten days from an attack of influenza, in which coughing was a prominent symptom. She then noticed general soreness in the abdomen, and this became more severe until a localized pain developed in the right lower quadrant. The abdominal wall did not move with respiration, and a sharply defined area of tenderness was evident in the outer margin of the rectus muscle, just below a line drawn from the umbilicus to the right anterior superior spine. Voluntary muscle spasm made rigidity doubtful. The patient lay curled up in bed. Her temperature was 100.5°F., leucocytes 16,500; polymorphonuclears 80 per cent. A diagnosis of appendicitis was made.

A right rectus incision was made. On splitting the sheath of the rectus, the muscle looked normal, but when its fibers were separated a cavity was found filled with clotted blood. Here the muscle fibers were torn and frayed; dark-grey and friable. There was no intraperitoneal disease.

Hilgenreiner reports a case of hematoma of the right rectus developing after influenza and in which the symptoms were even more alarming than those noted in Harris's case.

A woman aged 56 had arteriosclerosis. In 1922, she suffered from an attack of influenza, followed by prolonged coughing. There occurred a sudden, severe pain in the lower abdomen, accompanied by dyspnoea and vomiting, and with fecal and urinary retention. The symptoms were quite as severe as in peritonitis. After four days the pain localized in the right lower quadrant and a swelling, the size of a child's head, appeared. This, on aspiration, brought blood.

At operation a large space, filled with coagulated and fluid blood, was found beneath the right rectus sheath, and a portion of the muscle was torn across.

In 1926 Forbus wrote two most interesting papers on the pathological changes in voluntary muscle. The first article dealt with degeneration and regeneration of the rectus abdominis in pneumonia. The second was entitled "Experimental Study of Degeneration and Regeneration of Striated Muscle with Vital Stains." Both these papers merit careful reading by those interested in the degeneration and regeneration of muscle.

5. Heart Disease.

Heart disease undoubtedly has a share in the causation of hematoma of the rectus. Sometimes the cardiac condition appears to be the primary cause; more often the heart muscle seems to have been weakened by influenza or by bronchitis, as already mentioned.

Whittingdale's case is a striking example of cardiac disease accompanied by hemorrhage into the rectus muscle. A charwoman, aged 74, had been confined

to the house by a gradually progressive myocardial failure. She had had twelve children.

After being given digitalis and strophanthus, she vomited three times, and several days later, after repeated vomiting, was suddenly taken with violent pain in the right iliac region, complaining of a sensation as if something had given way. There was constipation and urinary retention. The lower right quadrant of the abdominal wall was rigid and tender.

The patient was in collapse and apparently moribund. A diagnosis of mesenteric embolus was made, and operation was not advised. The next day she was better, but a large swelling occupied the right abdomen, extending from the symphysis to the hypochondrium. The skin was ecchymotic; the mass was pyriform, with definite borders; it was firm and tender.

Operation disclosed oedema of the aponeurosis and beneath it a large mass of fluid and clotted blood, the evacuation of which left a large ragged cavity in the substance of the rectus muscle. The patient recovered.

6. Hemorrhagic Diathesis

This seems to have played a minor rôle in the development of hematoma of the rectus abdominis muscle. I know of only a single case, the one reported by Malpas in 1930.

Malpas' patient, a man aged 63, was admitted to the hospital with a provisional diagnosis of some form of intestinal obstruction. He gave a history of having suffered from chronic bronchitis for many years. Since childhood he had also been troubled with excessive bleeding after minor cuts and extraction of teeth. He had, indeed, been regarded by his relatives as a "bleeder." During a fit of coughing, he felt a sharp, intense pain in the left lower abdomen. The pain was severe for several hours during which time he vomited repeatedly. It then subsided into a persistent, dull ache. He was sent to the hospital on the third day of his illness.

An ill-defined, non-tender swelling was found in the abdominal wall corresponding in position to the left rectus sheath; it extended upward to the umbilicus and downward to the pubis. The overlying skin was normal, but there was a definite ecchymosis present over the left half of the scrotum. Apart from some evidence of chronic bronchitis, no other abnormal physical signs were found. The blood count was normal. The bleeding time was normal. On the eighth day of the illness, the pain recurred, the hematoma increased in size, and an exploration was decided upon.

At operation, the subcutaneous tissues were found to be normal, the rectus muscle itself was infiltrated with dark-brown blood clots, but no rupture of the muscle was seen. There was no free blood in the abdominal cavity. Removal of the clot was impossible owing to its intimate connection with the fibers of the

rectus muscle itself. There was very free oozing of blood from the muscle during the operation and hemostatic mattress sutures were necessary.

After the operation a slight but steady oozing of blood from the wound persisted for two days; it was treated with local pressure, and the subcutaneous injection of 10 cc. of normal horse serum. On the fourth day after operation he suddenly collapsed, vomited about two pints of dark blood, and died within an hour. No necropsy was performed.

7. *Surgical Operations*

Dr. Joseph B. De Lee when discussing Culbertson's paper said:

"I wish to call attention to one form of hematoma in the rectus muscle, or rather behind the rectus, which is not so uncommon as Dr. Culbertson has indicated, but which can occur after ordinary laparotomy. I use in my gynecological work, as well as obstetrical, the old 'trap-door' incision where the rectus muscle is pulled out of its sheath and afterward replaced. A relatively large branch of the deep epigastric artery is found, which ascends the posterior sheath of the rectus and enters the muscle about half way between its outer and inner border. The vessel is often ruptured by traction, causing a hematoma. I had one such case; on the second day the patient began to vomit, had a temperature of 102° and had all the signs of a beginning peritonitis. I found a hematoma behind the rectus muscle which made a distinct prominence in the peritoneal cavity, putting the peritoneum on the stretch and giving all the clinical signs of a peritonitis. We could not find the origin of the hemorrhage at that time, because the muscle was infiltrated with blood, but the main part of the blood was probably from the main branch of the deep epigastric artery."

I am glad Dr. De Lee drew attention to the possibility of hemorrhage from the deep epigastric, or from one of its branches, during an abdominal operation. If an assistant inserts his retractor under the rectus instead of under the peritoneum, he will often tear a small branch of the epigastric artery or vein, causing some bleeding. The same thing readily happens if the assistant draws the rectus muscle strongly to one side with his finger.

For over two decades I have drawn attention to this fact continually in the clinic. If one causes bleeding to occur under the rectus muscle, and does not check the bleeding, then I feel that a clotting may continue along the course of a vein and that this may be partly responsible for the phlebitis that is now and then noted in the leg a few weeks after operation. In our clinic, if there be the slightest evidence that

a branch of the epigastric is injured, it is immediately examined and tied if necessary.

8. Additional Causes

Gallbladder Disease. Where there is an old gallbladder infection there is undoubtedly some septic absorption, and this in turn tends to weaken the heart muscle as well as other muscles.

The literature contains reports of several cases in which the hemorrhage of the rectus was associated with infection of the gallbladder.

One of my patients had definite gallbladder trouble and also a large hematoma in the right upper abdominal wall. Both conditions were dealt with at the same time.

Tetanus. Case 15, referred to by Maydl, in his most illuminating article, was observed by Larrey, the famous French surgeon. The patient had tetanus; rupture of the rectus occurred above the umbilicus. The patient died. Whether the rupture was due to degeneration of the rectus or caused by the spasmodic contraction, or to a combination of the two, is, of course, impossible to determine.

Syphilis. Is said by some to have been a definite causative factor in the production of hemorrhage into the rectus muscle.

When the patient has been in a weakened condition, coughing, sneezing, lifting, or straining at stool, has sometimes been sufficient to cause a rupture of the rectus abdominis muscle.

TREATMENT OF HEMATOMA OF THE RECTUS ABDOMINIS MUSCLE

As a rule, it is necessary to cut down upon the hematoma, open up the sheath of the rectus, remove the clot and ligate any spurting vessel. Sometimes the blood is so intimately blended with the muscle that it can not be removed. When the bleeding comes from the muscle, then it may be necessary to use mattress sutures of catgut to check oozing. As a rule, the abdomen should not be opened unless there are coexistent, intra-abdominal complications. Where possible, the wound is closed without drainage; sometimes it is essential to drain. Where the hemorrhage has been slight no operation may be required.

In one of my cases in which we had both a hematoma and gallstones, I removed the blood clot and at the same time took out the gallstones.

SUMMARY

Hemorrhage into or beneath the rectus abdominis muscle is rather rare. It may take place in any part of the muscle, but is usually below the umbilicus.

In some cases the muscle is torn; in others, branches of the deep epigastric artery or vein have ruptured; in still other cases there has been both rupture of the muscle and also a tearing of one or more blood vessels.

As noted in Max Brödel's illustration, the posterior sheath of the rectus is missing in its lower portion; consequently, where the bleeding is below the navel, the blood usually lies between the muscle and the peritoneum. This causes peritoneal irritation and produces symptoms simulating in nearly every particular those of an acute abdominal lesion.

In those cases in which the sheath of the rectus has ruptured anteriorly, blood escapes into the fat and there may be an ecchymosis of the skin. In such cases a correct diagnosis may be made more readily.

In many of the cases recorded the operation was undertaken on the supposition that an intra-abdominal lesion existed and the true nature of the condition was detected only after the abdomen had been opened.

Sometimes rupture of the rectus muscle has been caused by direct violence; usually, however, the patient has for sometime been suffering from some debilitating disease, and a slight exertion has been followed by sudden abdominal pain with the development of the hematoma.

In typhoid fever and influenza there has often been an extensive waxy degeneration of the rectus muscle—Zenker's degeneration. In such cases the muscle has been brittle and has torn easily. This degeneration has undoubtedly been the causative factor in rupture of the muscle. In some gallbladder cases, in some cardiac cases, and in patients suffering from bronchitis, rupture has occurred. Hematoma of the rectus has occasionally been noted during pregnancy.

Treatment consists in removing the blood clot, in suturing the muscle, if necessary, and in tying any bleeding vessels.

The outlook in these cases is favorable provided the underlying general condition of the patient is good.

APPENDIX

ABSCESS BENEATH THE SHEATH OF THE RECTUS ABDOMINIS MUSCLE

1. In Cases of Influenza

In the foregoing pages we have seen that in many cases of typhoid fever a waxy degeneration of the recti and other muscles took place, and that in the course of a few weeks regeneration of these injured muscles began.

It has also been noted that Zenker's degeneration occurs in cases of influenza, and that in some of these cases infection of the degenerated muscle was also present. Thus one might, in the same rectus muscle, find small hemorrhages and also abscesses, and in some cases the abscess completely overshadowing the hemorrhage.

The following observations by Homer Gage and W. E. Ladd, are of particular interest in this connection, and will be quoted somewhat in detail.

Gage in his article which appeared in 1919, says (page 188):

"The most important complication of surgical interest which was met with in the epidemic of influenza last fall, as it was the most common, was undoubtedly empyema. Opportunity for its study and observation was not wanting in any community and reports have already been published from many quarters.

"Chief among these, in our experience at the Base Hospital at Camp Devens was a group of localized abscesses situated for the most part in tissues about the joints and in the muscles of the trunk.

"These abscesses appeared in the second or third week of the disease, in some even later, and were characterized by swelling and tenderness but no redness; joint motion was very painful and the appearance as well as symptoms suggested joint involvement.

"Of even greater interest were three cases of abscess in the sheath of the rectus abdominis muscle, interesting not only on account of their peculiar location but especially because we felt we could trace their development through its various stages."

Gage's case I occurred in a white male, 21 years old, who entered the hospital on September 16, with influenza. He had a definite pneumonia, apparently confined to the lower lobe of the right lung. At the end of the second week in October, when satisfactorily convalescent from pneumonia, he complained of pain and tenderness in the lower abdomen, and on the 19th presented a definite, globular swelling just above the pubes. This swelling was elastic but not movable. It suggested a large, tense bladder and, when that was ruled out, was still believed

to be intra-abdominal. The temperature was not over 100.5°. The patient presented no signs of general sepsis.

Incision revealed a large abscess involving the sheaths of both recti muscles. This healed promptly under simple drainage. Bacteriological examination showed a pure culture of pneumococcus, type I.

Gage's case II was in a colored male, 25 years old. He was admitted on September 12 with a diagnosis of influenza and had pneumonia of the left upper and right lower lobes. During convalescence, on the 29th of October, he developed a swelling in the midline between the umbilicus and symphysis, with slight pain, tenderness and fluctuation. The temperature was unaffected.

At operation, several ounces of pus were evacuated from the lower ends of the recti. The cultures revealed pneumococci which were not typed.

Gage's case III was in a white male, 24 years old, who entered the hospital on September 28 with influenza. He developed a pneumonia of the left lower lobe and of the right middle and lower lobes. Empyema of the left side followed. Pneumococci, type I, were found in the sputum and in the pleural exudate. On the 10th of November a submammary abscess of the right side was opened and from it staphylococci and streptococci were recovered on culture. The abscess cavity closed within a few days.

His general condition was good and there were no indications of general sepsis. On November 27, two months after his initial infection, he developed an abscess in the sheath of the rectus just above the symphysis. This contained a few ounces of thick pus which on culture yielded a pure pneumococcus, type I. Recovery was uneventful and prompt.

Gage says: "A quite similar case has been brought to my attention by Dr. W. E. Ladd of the Boston City Hospital, which occurred in his service last winter, and through his kind permission the records have come into my possession.

"It was that of a girl, ten years old, who was admitted December 8, with influenza; additional diagnosis, pneumonia, right upper lobe, with return to normal temperature on the 20th; then had suppurative otitis media, not severe, and on January 8 complained of pain and tenderness in lower abdomen. Incision revealed an abscess confined to the recti muscles, containing Gram-positive streptococci, which healed without complication.

"The last case differs from the others only in that the infecting organism was a streptococcus instead of a pneumococcus.

"In these four cases we find influenza, followed by a secondary infection, limited to the recti muscles without any of the general symptoms or of the multiple lesions that usually accompany pyaemic processes.

"We are at once reminded of the degeneration of the abdominal muscles which has been often noted as a complication of typhoid fever, was first described by Zenker, in 1864, and bears his name, and which has been fully described by our own Dr. Keen in his Toner Lecture, 'On the Surgical Complications of Typhoid,' in 1876."

2. In Cases of Typhoid Fever

Abscess of the abdominal wall after typhoid is evidently much less common than after influenza. W. W. Keen, however, in his well-known book on surgical complications and sequelae of typhoid fever, reported a case of abscess of the abdominal wall after typhoid.

On page 167 he says: "D. C., aged 27, was admitted to St. Agnes Hospital, June 29, 1891. On March 7, 1891, he had been taken sick with typhoid fever and was in bed until April 27. On May 29 he again fell ill with what was pronounced a relapse. About June 20 he suffered considerable pain in the lower abdomen. This was soon followed by swelling which increased quite rapidly. On admission nine days afterwards, a swelling 9 cm. long was found just above the pubes, apparently in the right rectus. It was quite tender. His temperature was 102°.

"July 4, I made an incision into the abscess, and found that it not only occupied the muscle, but also extended into the lower abdomen and pelvis, reaching to the bladder and rectum. It had not, however, ruptured into the peritoneal cavity, but had pushed the peritoneum before it. Over a pint of pus was evacuated.

"In a little over twenty-four hours the temperature fell to normal and in twelve days he went home."

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THE CORRELATION OF THE RESPIRATORY QUOTIENT TO GLYCOGEN RESERVES[1]

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It is well known from animal experiments that a diet rich in carbohydrate foods induces not only a deposition of large amounts of glycogen in the liver, but also a respiratory quotient which approaches unity; on the other hand, the ingestion of little or no carbohydrate food is accompanied by a respiratory quotient which falls to 0.70–0.75, and under these conditions the liver contains only small quantities of glycogen. Although these simple facts have been recognized since the pioneer works of Claude Bernard and Carl Voit, no definite correlation between these various factors has heretofore been made. The experiments reported below suggest that these associations represent more than incidental relationships. Provided the determinations were made under conditions of absorptive equilibrium, a definite correlation was found between the respiratory quotient and the glycogen content of the liver.

METHODS

The experiments are extremely simple. Under only procaine anaesthesia, a specially designed tracheal cannula can be inserted into a rabbit with scarcely any disturbance. When placed in a small box on a high stool, rabbits will sit quietly for hours at a time. After allowing 2–4 hours for quiet and equilibrium to be regained, the expired air is collected in two periods of 20–30 minutes each, blood is taken from the ear vein for the estimation of sugar and carbon dioxide combining power, and the animal killed by a quick injection of urethane. Of this drug 1.5 gms. per kilo of body weight induce almost instantaneous and complete anaesthesia in rabbits without the phase of excitement and struggling so commonly experienced with other anaesthetic drugs. Thin slices of liver, roughly freed from blood, were placed in a weighed amount of 30% KOH, the legs were

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amputated by a rapid clean cut and placed in brine chilled to minus 13–15°C., the samples being taken after thorough freezing. The time elapsing between the injection and the removal of the tissue samples was constant throughout, and was so brief that the effect of the drug on glycogen has been ignored.

In order to obtain the necessary range of liver glycogen values, several dietary regimes were employed. The standard diet for a rabbit consisted of 2 ounces of "Domino Rabbit Pel-ets"[2] a day, with chopped alfalfa and water in the cage constantly. To secure the low respiratory quotient range, periods of starvation lasting 1–5 days were employed. For the middle range, the standard diet was followed by 6–12 hours of starvation. The high points were obtained by feeding a concentrated diet of "Pel-ets" only, followed by a rest period of 3 hours, the minimum necessary to insure adequate recovery from the effects of inserting the tracheal cannula. The extreme high values were obtained by giving, in addition to the diet of "Pel-ets," large quantities of 25% cane sugar by stomach tube. Since rabbits tend to eat throughout the day, there is never a true post-absorptive period comparable to that in human subjects. This characteristic, however, proved a distinct advantage in the present experiments in which *absorptive equilibrium* was more important than true post-absorptive phase. Since the diet is known to have an effect on the acid-base equilibrium and on carbohydrate metabolism, blood was taken for the estimation of carbon dioxide combining power as a check on this possible factor.

Blood sugar was determined by the Hagedorn-Jensen method (1). The technique of Good, Kramer and Somogyi (2) was followed for glycogen estimation, the final sugar titration being made by the Hagedorn-Jensen method. Expired air was analyzed in the usual manner in a Haldane gas analysis apparatus. Carbon dioxide combining power was determined by the Van Slyke manometric method (1). The macro-Kjeldahl technique was followed for determining urinary nitrogen.

RESULTS

For purposes of statistical analysis, the 119 animals have been grouped according to the respiratory quotient. Table I shows the number of animals in each group and the average values obtained. It should be noted that the average values for blood sugar and CO_2 combining power are not significantly different in the various groups

[2] "Domino Rabbit Pel-ets" are composed, according to the manufacturers, Nowak Milling Corporation of Hammond, Indiana, of "dried buttermilk, 2% cod liver oil, fine ground rolled oats, fine ground oats, old process linseed oil meal, corn germ oil meal, yellow corn feed meal, ground wheat, alfalfa leaf meal, fine ground barley, 2% calcium carbonate, 2% steamed bone meal, ½ of 1% iodized salt,—protein 12%, fat 4%, fiber 10%."

except in the former instance, when free sugar was forced in order to secure the extreme high R.Q. values. Under these conditions the blood sugar was higher than the usual fasting level for rabbits, *viz.* 100–125 mgms. In general, as would be expected, the respiratory quotient depends on the length of the fasting period.

When the respiratory quotients of the individual rabbits are plotted against the corresponding values for liver glycogen, a relationship is immediately apparent. In Chart 1 it will be seen that the high R.Q. values are consistently associated with a high liver glycogen, and low R.Qs. with low glycogen. The spread from the

TABLE I

Summary of the data obtained on a series of normal rabbits under conditions of absorptive equilibrium

NUMBER RABBITS	AVERAGE						
	FASTING R.Q.	PERIOD OF STARVATION	BLOOD SUGAR	BLOOD CO_2	Muscle glycogen	Liver glycogen	Liver glycogen
		hour	*mgm.*	*vol. per cent*	*per cent*	*per cent*	*gram per kilo*
5	0.68	96	125	53	0.52	1.65	0.53
19	0.733	44	114	48	0.62	1.56	0.53
16	0.785	18	111	51	0.81	2.27	0.82
16	0.831	12	107	53	0.87	3.56	1.53
17	0.88	11	123	53	0.99	5.93	2.77
17	0.928	5	111	50	1.10	9.41	4.80
23	0.978	7	177	47	1.30	12.2	7.43
6	1.03	0	194	46	1.28	14.5	11.0

mean value is, however, considerable. This is, no doubt, influenced by the fact that *percentage* of liver glycogen does not take into account the variations of individual animals in the size of the liver with respect to body weight. An attempt was made to correct this obvious source of error by using total liver glycogen in grams per kilo of body weight instead of percentage values. And in order to make the figure for body weight represent active tissue, in so far as possible, the weight of the intestinal tract and contents was deducted from the observed weight of the animal. The weight of the bowel was considered to balance roughly the scattered inactive fat of the tissue depots. This figure for *net* body weight served as the basis for

Chart 2, in which the respiratory quotients are plotted against the total grams of liver glycogen per kilo of net body weight. The same relationship is again apparent, and the scattering is somewhat less than in Chart 1. In addition, it should be noted that when the respiratory quotient is below 0.80, the level of protein combustion, the liver glycogen has already fallen to an essentially minimum level.

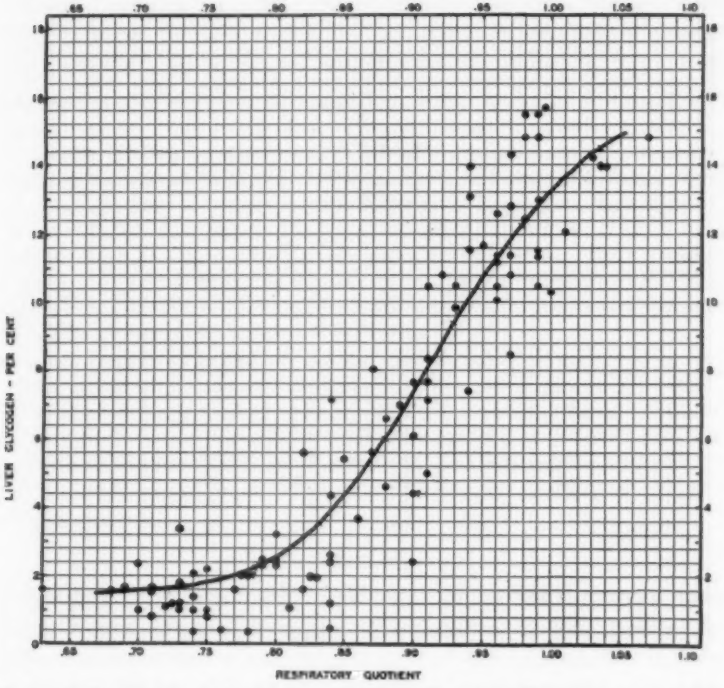

CHART 1. SHOWING THE PERCENTAGE OF LIVER GLYCOGEN PLOTTED AGAINST THE RESPIRATORY QUOTIENT OF 119 NORMAL RABBITS UNDER CONDITIONS OF ABSORPTIVE EQUILIBRIUM

The amount of scattering from the average values in Chart 2 suggests that other factors probably influence the relationship, and it is obvious that such is the case. In the absorptive period before equilibrium has been reached, a high blood sugar induces increased carbohydrate combustion and a high respiratory quotient long before

the glycogen reserves become filled. Regardless of the actual rate of absorption, whether negligible, as in prolonged starvation, or proceeding at a maximum rate, as in the case when large amounts of sugar are put into the stomach, a state of relative equilibrium between the absorption into the blood stream and its removal by the tissues is established after several hours. Such a phase is called, for want of a better term, "absorptive equilibrium." Although precau-

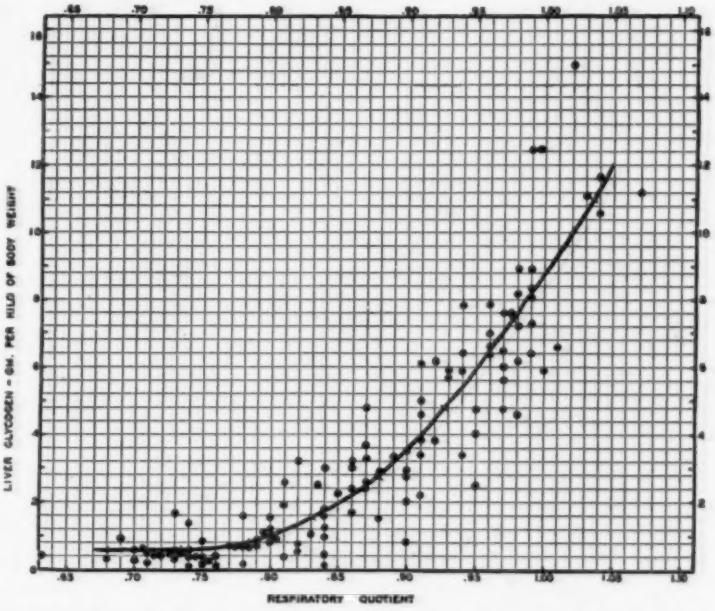

CHART 2. SHOWING THE TOTAL GRAMS OF LIVER GLYCOGEN PER KILO OF NET BODY WEIGHT PLOTTED AGAINST THE RESPIRATORY QUOTIENT

tions were taken in the present group of animals to allow this state to be reached before making the determinations, it seems probable that some of the scattering observed in the charts may be due to the fact that true equilibrium was not really established. The effect of nitrogen metabolism on the R.Q. is usually calculated from the nitrogen excretion during the experimental period. This was obviously impractical under the present conditions. However, in a sepa-

TABLE II

Average nitrogen excretion of rabbits per kilogram of net body weight per 24 hours

DIET	NUMBER EXPERIMENTAL DAYS	AVERAGE NET WEIGHT	NITROGEN EXCRETION PER KILOGRAM PER 24 HOURS	LIMITS OF VARIATION
		kg.	*gram*	
"Pel-ets" only	12	2.49	0.33	0.23–0.36
Stock diet	23	1.92	0.50	0.20–0.91
Starvation 0 –24 hours	12	2.01	0.34	0.25–0.40
Starvation 24–48 hours	12	1.98	0.45	0.31–0.60
Starvation 48–72 hours	11	1.64	0.65	0.17–0.97
Starvation 72–96 hours	8	1.56	0.51	0.20–0.75
Starvation 96–120 hours	6	1.49	0.43	0.20–0.54

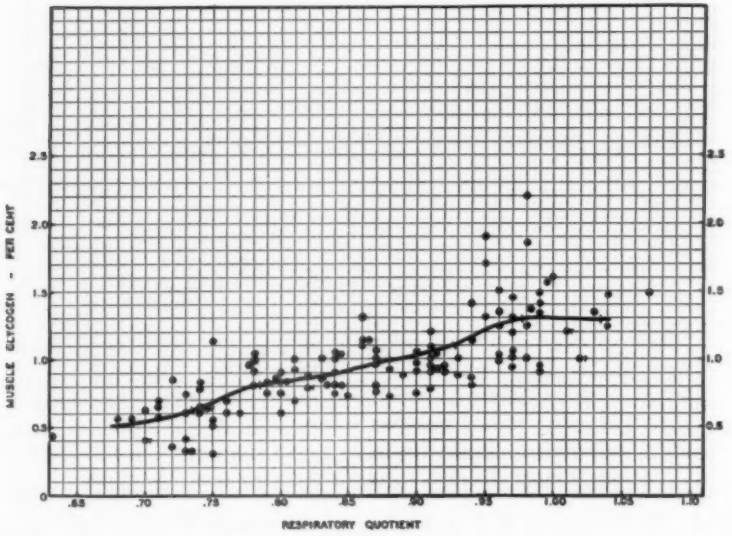

CHART 3. SHOWING THE PERCENTAGE OF MUSCLE GLYCOGEN PLOTTED AGAINST THE RESPIRATORY QUOTIENT OF 119 NORMAL RABBITS UNDER CONDITIONS OF ABSORPTIVE EQUILIBRIUM

rate group of animals, the nitrogen excretion was studied during starvation and while eating the same diets as were employed in the group used for glycogen and R.Q. determinations. In Table II

these results are available, but no attempt has been made to correct the figures for respiratory quotients, which, as plotted, are those obtained by direct analysis of the expired air. It should be noted that the variations in nitrogen excretion are considerable, which, no doubt, also accounts for some of the spreading effect seen in Charts 1 and 2. Hyperventilation seems an unlikely source of error, since the animals were continuously connected to the respiration appara-

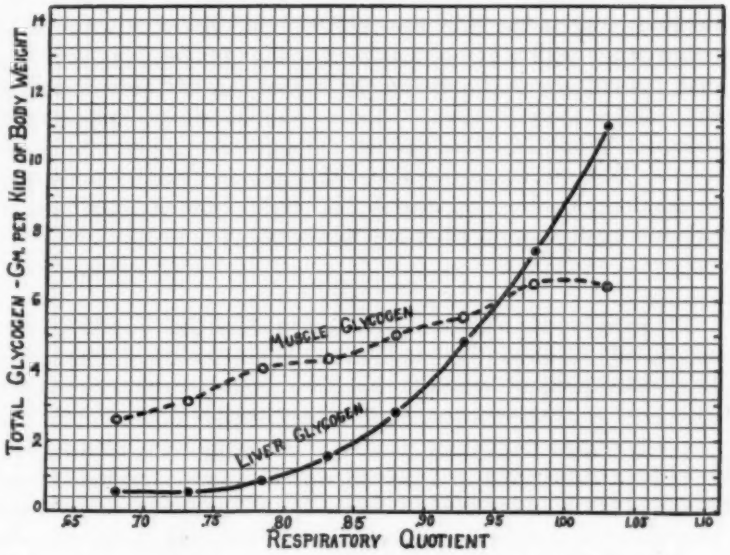

CHART 4. SHOWING THE AVERAGE VALUES FOR TOTAL LIVER AND TOTAL MUSCLE GLYCOGEN PER KILO OF NET BODY WEIGHT PLOTTED AGAINST THE RESPIRATORY QUOTIENT OF 119 NORMAL RABBITS

tus for a total of several hours, and respiration periods were obtained in duplicate. Postmortem glycogenolysis gives, of course, a constant error which is unmeasurable and unavoidable in some degree. But, in spite of these numerous possibilities for variation and error, the fact still remains that under conditions of absorptive equilibrium, liver glycogen seems to be related to the respiratory quotient.

In Chart 3 the respiratory quotient is plotted against the percentage of muscle glycogen. A relationship is not so clearly defined

as in the previous charts. Even when muscle glycogen is plotted as total quantity in grams per kilo of net body weight,[3] as in Chart 4, the relationship is distinctly different from that obtained in the case of liver glycogen. While there is a definite tendency for muscle glycogen to be increased in the range of high R.Q. values, and decreased when the R.Q. is low, the change is not a consistent one throughout. At the lower end of the curve, *viz.* R.Q. of 0.75 and below, the average line assumes a different grade, falling off rather sharply. And at the R.Q. values of 0.95 and above, so much scattering occurs with a known maximum value of 2.4–4.0 per cent (3), that some doubt is thrown on the consistency of the relationship which at first seems apparent. And, in addition, the very pronounced effects of insulin (4, 5) and of adrenalin on muscle glycogen (4, 6) lead one to suspect that the relationship seen in Charts 3 and 4 may be more apparent or accidental than real. However, the present data are inadequate to allow any final conclusion to be drawn.

DISCUSSION

The experiments reported above demonstrate that in rabbits during periods of absorptive equilibrium, a definite correlation exists between respiratory quotient and liver glycogen; the correlation with muscle glycogen is less distinct, and possibly dependent on factors other than respiratory quotient. Although such results could have been anticipated in a general way because of the well known effects of fasting and forced feeding on both respiratory quotient and liver glycogen, the differences between the two great glycogen depots in respect to R.Q. are somewhat surprising, in view of the fact that muscles constitute approximately 45 per cent of the total weight of rabbits, and should account for an even larger proportion of the total energy expenditure. On the other hand, the liver, which represents only 4–10 per cent of the total weight, would hardly be expected so to dominate the combustion of the body that the respiratory quotient would follow closely upon its level of glycogen reserve. The

[3] In 5 rabbits the muscles were carefully dissected away from the bones and other tissues and found to average 44% of the gross weight, and 53% of the net weight of the animal. Because of individual variations and difficulties in making such dissections complete and accurate, the round number of 50% has been used in the calculations.

explanation for such a state of affairs is by no means clear. A correct interpretation will await further investigations of the intermediary metabolism of carbohydrates and fats, and of the rôle of such substances as glycogen, creatine phosphate and lactic acid in the energy transformation in muscles.

From the *clinical point of view*, the results are of practical interest. Heretofore, no method has been available for even approximating the glycogen reserves in the liver of human beings. The present findings, as well as other studies now being conducted on human subjects, suggest that variations in the fasting respiratory quotient are associated with corresponding changes in glycogen reserves. Thus, in an individual patient, the finding of a high fasting respiratory quotient at one phase of a disease and a low value at another, probably signifies different levels of liver glycogen. Such determinations would be particularly helpful in evaluating the effects of undernutrition in disease, and might offer a lead toward a better understanding of the factors involved in producing the sum total of the symptoms.

CONCLUSIONS

In normal unanaesthetized rabbits, the respiratory quotient obtained during absorptive equilibrium shows a definite correlation with the glycogen reserves in the liver. Muscle glycogen correlates less clearly with the respiratory quotient.

In view of this and of other observations to be reported later, it is suggested that in human subjects, the fasting respiratory quotient offers a method of approximating the reserves of glycogen in the liver.[4]

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[4] The writer is indebted to Miss Jane Gundersheimer and Miss Barbara Ottinger for technical assistance in carrying on the studies.

THE PRESENCE OF MULTIPLE AGGLUTININS IN THE SERUM OF PATIENTS WITH CHRONIC RHEUMATOID ARTHRITIS

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In 1931 Nicholls and Stainsby reported the presence of agglutinins in the sera of patients suffering from chronic rheumatoid arthritis for their "typical strains" of hemolytic streptococci isolated from the blood stream and joints of such patients (1). This finding was interpreted as lending strong support to the view that these "typical strains" were an important etiological factor in chronic rheumatoid arthritis. The following year Dawson, Olmstead and Boots (2) demonstrated that this property was not confined to the "typical strains" of Nicholls and Stainsby, but was present for other strains of hemolytic streptococci of human origin and for rough strains of pneumococci as well. Furthermore, by absorption with any one of the strains of hemolytic streptococci used they were able to remove completely, or nearly so, the agglutinins present in a given serum for other strains of hemolytic streptococci, and the agglutination of rough pneumococci was appreciably reduced by the absorption with hemolytic streptococci. On the other hand, absorption with rough pneumococci failed to remove the agglutinins for hemolytic streptococci, although the titre was to some extent reduced. McEwen, Chasis and Alexander (3) later found that the sera of patients suffering from chronic rheumatoid arthritis at times gave cross agglutination reactions with hemolytic streptococci of groups A, B, C, D and E of Lancefield's classification. Further, they were able to demonstrate crossing in precipitation reactions, occasionally with extracts of all groups and frequently with those of groups A, B and G. They interpreted these cross reactions as due possibly to (1) a lack of true antigen-antibody nature of the reaction, (2) anamnestic responses on the part of patients who had previously harbored hemolytic streptococci of different groups, and (3) the presence of multiple antigens in their extracts and a varying capacity of individuals to form multiple antibodies following infection. To these investigators the last explanation seemed most probable. Upon amplifying these studies Chasis and McEwen concluded that the cross precipitation reactions obtained were probably due to the presence in the sera of patients with rheumatoid arthritis of antibodies against a non-group-specific fraction or radical present in the bacteria and their crude C extracts. Dawson, Olmstead and Jost (6) found a close parallelism between the ability of rheumatoid arthritis sera to agglutinate

group A hemolytic streptococci and to precipitate group-specific nucleoprotein and carbohydrate fractions of the same organism. They felt that this fact lent support to the view that both reactions were truly immunological in nature and not due to some nonspecific physico-chemical property of the serum. They emphasize, however, that the reactions are only group-specific in nature and cannot be interpreted as strain specific. Later Dawson and Olmstead examined sera from a large group of patients suffering from chronic rheumatoid arthritis for agglutinins and precipitins for representative strains of all of the serological groups of hemolytic streptococci of Lancefield's grouping. They found, as before, well defined agglutination reactions with group A organisms and little or no agglutination with organisms other than group A. They felt, therefore, that these results indicated that the agglutination of hemolytic streptococci in rheumatoid arthritis sera was highly characteristic of group A. Precipitin reactions were again well defined with group A organisms, whereas crossing of the reaction from one group to another was minimal. What crossing they obtained, however, was with groups B and G. These observers concluded that any crossing they had observed in these reactions could be accounted for by the presence of common antigenic constituents in the various groups and that both agglutination and precipitation reactions in rheumatoid arthritis sera were characteristic for group A hemolytic streptococci.

We have selected the sera of 25 patients suffering from chronic rheumatoid arthritis which showed agglutinins for hemolytic streptococci of human origin, or group A strains, beyond question. These sera were tested against AB_{13}, "a typical strain," obtained from Cecil, Nicholls and Stainsby, and against the scarlet fever strain, NY_6. It was found that the agglutination reaction was, with only slight variations, identical with these two organisms. The reactions on the whole tended to be more pronounced with heat-killed antigens than with living ones but were definite in most instances to a titre of 1:1280, as far as the dilutions were carried. In these tests and all subsequent ones agglutinations which could be clearly discerned with the eye were recorded as ++ and any clumping requiring a glass to establish was recorded as one plus.

These sera were then examined for agglutinins for three group B strains of hemolytic streptococcus, K158B, K107 and V-8. Agglutinins were found in all of the sera for K107. These reactions were in all instances definite in a dilution of 1:160 or more, but in most instances did not react to dilutions obtained with group A strains. Here again the reaction with heat-killed organisms was generally stronger than

that obtained with living organisms. It was found with K158B and V-8 that in some instances no agglutination was obtained. In those

TABLE 1

		AGGLUTINATION TESTS							°C.
		1:20	1:40	1:80	1:160	1:320	1:640	1:1280	
I	AB_{13} a	++	++	++	++	++	++	+	0
	AB_{13} hk	+++	++	++	++	++	+	+	0
II	NY_5 a	++	++	++	++	+	+	+	0
	NY_5 hk	++	++	++	++	++	+	?	0
III	K158 a	+	+	+	+	+	0	0	0
	K158 hk	+	+	+	+	+	0	0	0
IV	K107 a	++	+	+	+	?	0	0	0
	K107 hk	++	+	+	?	0	0	0	0
V	V-8 a	++	+	+	+	+	?	0	0
	V-8 hk	++	+	+	+	+	+	0	0
	Alpha Strep. a	?	0	0	0	0	0	0	0
	Alpha Strep. hk	+	?	0	0	0	0	0	0
	PnI a	0	0	0	0	0	0	0	0
	PnI hk	0	0	0	0	0	0	0	0
	PnIII a	0	0	0	0	0	0	0	0
	PnIII hk	0	0	0	0	0	0	0	0
	B. dys. (Flexner) a	0	0	0	0	0	0	0	0
	B. dys. (Flexner) hk	0	0	0	0	0	0	0	0
	B. proteus a	0	0	0	0	0	0	0	0
	B. proteus hk	0	0	0	0	0	0	0	0
	B. coli a	0	0	0	0	0	0	0	0
	B. coli hk	0	0	0	0	0	0	0	0

Type of response shown by rheumatoid arthritic sera to tests for agglutinins for Group A and Group B hemolytic streptococci and other bacteria. I and II are Group A, and III, IV and V are Group B hemolytic streptococci.

sera giving the agglutination reaction it was generally less definite and obtained in lower dilutions than that obtained with K107, but

V-8 was generally more responsive than was K158B. In all of these tests dilutions of serum from 1:20 to 1:1280 were made. A twenty-four hour broth suspension of organisms was prepared and added in equal quantity to the dilutions of serum. The tubes were then placed in the waterbath at 56°C. for two hours and read the following morning after remaining in the icebox over night. Tests were run with washed suspensions of organism resuspended in normal salt solution as well as with broth suspensions, but no difference in the reaction was discernible.

The same sera were then examined for agglutinins for Alpha Streptococci, Type I pneumococci, Type III pneumococci, B. dysenteriae (Flexner), B. proteus and B. coli. Only occasional reactions were obtained with any of these organisms but one, and when obtained were present only in low titre, not exceeding 1:80 and usually lower. The exception was Type III pneumococcus. The strain of Type III pneumococcus first used was a stock strain and its physical characteristics were not known. However, when a freshly isolated strain of Type III pneumococcus was used, the reaction was not obtained, and none of the sera gave the type-specific precipitin reaction for the Type III pneumococcus.

The same arthritic sera were then absorbed with representative strains of the two serological groups of hemolytic streptococci A and B, using AB_{13} for group A and K107 for group B. Absorptions were also carried out with Type III pneumococcus. A generous amount of twenty-four hour broth cultures of AB_{13}, K107 and Type III pneumococcus were added to separate portions of a 1:5 dilution of the serum and placed in a water bath at 56°C. and frequently agitated for two hours. These suspensions were then placed in the icebox and allowed to remain from one to four days. Appropriate dilutions were then made using the absorbed serum and agglutination tests run in the same manner as the previous ones. It was found that in all instances agglutinins previously present for the absorbing organism were entirely removed. Further agglutinins previously demonstrated as present for other members of the same serological group were either definitely reduced or entirely removed. However, when the absorbed serum was tested for agglutinins for hemolytic streptococci of the other group in question it was found that they were unaffected by the

TABLE 2

		ABSORPTION TESTS							°C.
		1:20	1:40	1:80	1:160	1:320	1:640	1:1280	
I	AB_{13} a	++	++	++	++	++	+	+	0
	AB_{13} a (AB_{13} ab)	0	0	0	0	0	0	0	0
	AB_{13} a (K107 ab)	++	++	++	++	++	+	+	0
	AB_{13} a (PnIII ab)	++	++	++	++	++	+	+	0
II	AB_{13} hk	+++	++	++	++	++	+	+	0
	AB_{13} hk (AB_{13} ab)	?	0	0	0	0	0	0	0
	AB_{13} hk (K107 ab)	+++	++	++	++	++	+	+	0
	AB_{13} hk (PnIII ab)	++	++	++	++	++	+	+	0
III	NY_5 a	++	++	++	++	+	+	+	0
	NY_5 a (AB_{13} ab)	+	+	0	0	0	0	0	0
	NY_5 a (K107 ab)	++	++	++	++	+	+	+	0
	NY_5 a (PnIII ab)	++	++	++	++	+	+	+	0
IV	NY_5 hk	++	++	++	++	++	+	?	0
	NY_5 hk (AB_{13} ab)	+	+	0	0	0	0	0	0
	NY_5 hk (K107 ab)	++	++	++	++	++	+	?	0
	NY_5 hk (PnIII ab)	++	++	++	++	++	+	+	0
V	K158B a	+	+	+	+	+	0	0	0
	K158B a (AB_{13} ab)	+	+	+	+	+	?	0	0
	K158B a (K107 ab)	+	?	0	0	0	0	0	0
	K158B a (PnIII ab)	+	+	+	+	+	?	0	0
VI	K158B hk	+	+	+	+	+	0	0	0
	K158B hk (AB_{13} ab)	+	+	+	+	+	0	0	0
	K158B hk (K107 ab)	0	0	0	0	0	0	0	0
	K158B hk (PnIII ab)	+	+	+	+	+	0	0	0
VII	K107 a	++	+	+	+	?	0	0	0
	K107 a (AB_{13} ab)	++	+	+	+	+	?	0	0
	K107 a (K107 ab)	0	0	0	0	0	0	0	0
	K107 a (PnIII ab)	++	+	+	+	+	0	0	0
VIII	K107 hk	++	+	+	?	0	0	0	0
	K107 hk (AB_{13} ab)	++	+	+	+	0	0	0	0
	K107 hk (K107 ab)	?	0	0	0	0	0	0	0
	K107 hk (PnIII ab)	++	+	+	+	?	0	0	0
IX	V-8 a	++	+	+	+	+	?	0	0
	V-8 a (AB_{13} ab)	++	+	+	+	+	+	0	0
	V-8 a (K107 ab)	+	?	0	0	0	0	0	0
	V-8 a (PnIII ab)	++	+	+	+	+	?	0	0

TABLE 2—*Concluded*

		ABSORPTION TESTS							°C.
		1:20	1:40	1:80	1:160	1:320	1:640	1:1280	
X	V-8 hk	++	+	+	+	+	+	0	0
	V-8 hk (AB_{13} ab)	++	+	+	+	+	+	0	0
	V-8 hk (K107 ab)	?	0	0	0	0	0	0	0
	V-8 hk (PnIII ab)	++	+	+	+	+	+	0	0
	PnIII a	0	0	0	0	0	0	0	0
	PnIII a (AB_{13} ab)	0	0	0	0	0	0	0	0
	PnIII a (K107 ab)	0	0	0	0	0	0	0	0
	PnIII a (PnIII ab)	0	0	0	0	0	0	0	0
	PnIII hk	0	0	0	0	0	0	0	0
	PnIII hk (AB_{13} ab)	0		0	0	0	0	0	0
	PnIII hk (K107 ab)	0	0	0	0	0	0	0	0
	PnIII hk (PnIII ab)	0	0	0	0	0	0	0	0

Type of response shown by rheumatoid arthritic sera to absorption with Group A and Group B strains of hemolytic streptococci and with Pn. III. I, II, III and IV represent the agglutination of Group A strains after these absorptions. V, VI, VII, VIII, IX and X represent agglutination of Group B strains after these absorptions.

heterologous absorption. Thus, a given serum absorbed with AB_{13}, a group A strain, was found to contain no agglutinins for AB_{13}, and those for NY_5, belonging to the same serological group, were either markedly reduced or entirely removed, whereas the agglutinins for group B strains, K107, K158B, and V-8 were unaffected. In like manner absorption of this serum with K107, a group B strain, entirely removed agglutinins for this strain and in most instances entirely removed those for K158B and V-8, members of the same serological group. However, the agglutinins for AB_{13} and NY_5, both members of group A, were unaffected by the absorption. Further, when the serum was absorbed with Type III pneumococcus any agglutinins present for that organism were removed, whereas agglutinins for AB_{13} of group A, and K107 of group B were unaffected or slightly diminished but not removed.

It has been repeatedly demonstrated that normal serum contains no significant agglutinins for hemolytic streptococci or pneumococci and we made no further effort to substantiate this observation. However, in order to test the particular organisms that we were using, ten normal sera from prospective blood donors were examined for agglutinins

for AB_{13}, K107 and Type III pneumococcus. In all instances no agglutinins were found for the organism used in these tests.

DISCUSSION

These investigations would indicate that the agglutination of hemolytic streptococci is quite characteristic of well established chronic rheumatoid arthritis, but is not confined to streptococci from human sources, or group A organisms. It is present for certain strains of hemolytic streptococci of other than human origin and, in this study, for three strains of group B of Lancefield's serological classification. The fact that absorption with a representative strain of one group will not only remove the agglutinins for that strain but also for others of the same group points strongly to a group specificity of the reaction rather than to a strain specificity. Dawson and his coworkers have demonstrated this with group A streptococci and it now seems equally true for group B strains, and that the agglutinins for each group are separate and apart one from the other. It would seem unlikely that such regular complete dissociation of agglutinins as we have found would be obtained were the agglutinins present in these sera due to anamnestic response on the part of individuals who had formerly harbored hemolytic streptococci of groups other than group A. It is, of course, possible that the true antigen-antibody nature of the reaction may still be questioned but, again, one would not expect such selectivity as here seems to be the case.

It would seem, therefore, that the phenomenon here observed is most probably explained by the development of multiple agglutinins for hemolytic streptococci in the sera of persons suffering from chronic rheumatoid arthritis rather than to any crossing of the reaction between the two groups studied. Whether or not such reactions are peculiar to group B hemolytic streptococci we are unable to say, as other serological groups have not been studied. The present study does not bar the conclusion that the agglutinins present in these sera are the result of rheumatoid arthritis, and are, indeed, quite characteristic of the disease, but the true nature of the reaction in this disease requires further study.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Post-Mortem Appearances. By JOAN M. ROSS. 3rd ed. 243 pp. $2.50. (*Oxford Medical Publications, Oxford University Press, New York and London, 1937.*)

This pocket-sized book, which is now in its third edition, describes the various gross pathological changes met with in the autopsy room. It is clearly written and has an adequate index. It can be recommended as a useful aid to the student who is beginning the study of pathology.

R. H. F., JR.

An Investigation into Questions of Social Hygiene in the Counties of Västerbotten and Norbotten, Sweden. Conducted with the support of the Royal Medical Board in 1929–1931. Published in Swedish in 1934. English, partly revised edition, 780 pp. Illus. (*Hakan Ohlsson, Lund, 1937.*)

This report consists of a series of investigations regarding the hygienic conditions in the two most northern counties of Sweden. Nearly half of the country lies above the Artic Circle, and its western half is Lapland. The investigations were undertaken primarily to ascertain the effects of dietary deficiency, but they spread to a more general consideration of the causes of sickness having their origin in the social maladies of this country, where life is particularly hard, and where resources and modern developments are just beginning to penetrate. Poverty, malnutrition, long and badly arranged working hours, bad housing and injurious habits and customs were studied in their relation to the health of the people.

The report is presented in five parts, the first of which gives an interesting description of the country and its climate, with general observations on the housing and mode of life of the rural population, and the results of the medical examination of school children. The second part is a description of the diseases in Upper Norrland, the most northern part of Sweden, with special reference to the composition of the diet. Here many people live on a meal-milk diet, consisting exclusively of flour, milk, potatoes and a little butter. Investigations of the nutritional conditions of the population, the basal metabolism in relation to diet, the incidence of achylia gastrica and of anemia are among those reported in this part of the study.

The third deals with the condition of the teeth and dental diseases, and attention is directed especially to the effect of hypovitaminosis in producing diseases of the teeth and mouth. The subject of the lack of vitamines in the diet is taken

up especially in the fourth part of the report, in which the determinations of the antiscorbutic potency of vegetable products, chiefly berries grown in Norrland, is reported. The fifth part relates to improvements in hygiene which are recommended for this country on the basis of the investigations, with suggestions and guidance for local government officials. The original Swedish report also contained a section giving advice to housewives, which was not included in the English edition.

The report has a number of interesting features beside a great mass of scientific data gathered under the auspices of leading scientific workers of Sweden. The investigations have been carried on by doctors of medicine, dentists, agriculturists, educators and government officials in other fields. The report contains much scientific information on a large number of people living under extremely adverse social and hygienic conditions and therefore has unique qualitites. It is of interest also that an attempt has been made to have the findings of the studies become immediately applicable to the people, by directing the last part of the report toward lay persons, whose responsibility it is to effect as many of the needed reforms as is possible. The recommendations cover the following measures for improvements in the health services:

a. Maintenance and inspection of dwellings, and the housing problem.
b. Care of the health of infants and small children in their homes, and maternity welfare.
c. Care of the health of children of school age.
d. The diet problems in Upper Norrland.
e. Dental services for school children and adults.
f. Gardening, with reference to conditions in Upper Norrland.

G. C. R.

A Century of Medicine in San Antonio, By PAT IRELAND NIXON, M.D. 405 pp. Pl. $4.00. (*Privately published by the author, San Antonio, Texas, 1936.*)

This is the story of medicine in Bexar County, Texas, from the days when there was little to record to the present with its flourishing, well equipped profession, unusually well organized in the Bexar County Medical Society, that owns its home and houses a modern medical library.

The early history has much to do with the struggles of Texans in general in which the physicians bore their part well. Pollard, Michison and Thompson died at the Alamo along with Travis, Bowie and Crockett. With the growth and development of Texas the narrative becomes that of medical men and events almost exclusively. During the latter half of the 19th century, medicine in southwest Texas was dominated by two remarkable men, Dr. George Cupples and Dr. Ferdinand Herff, a Scot and a German, general practitioners both, but with a strong bent for surgery. How these striking personalities must have rejoiced in their great experience of passing from the dreary wilderness of surgery without benefit of asepsis or anaesthesia to the promised land of vastly increased opportunities!

The book shows evidence of careful and painstaking research. The author graduated at the Johns Hopkins Medical School in 1909 and began practice in San Antonio two years later, just eight years after the organization of the Bexar County Medical Society as the successor of the Western Texas Medical Association. He has had no small part in building up the strength of organized medicine in his community.

The book is readable even for one without special local interests. A possible tedium has been relieved by the appropriate insertion of many anecdotes with a strong medical tinge, some of them racy enough. The reviewer wishes for the book a good sale, with many dollars for the Bexar County Medical Society to which the profits are dedicated.

T. P. S.

Pathology of the Central Nervous System. By CYRIL B. COURVILLE. 344 pp. Illus. $5.75. (*Pacific Press Publishing Assn., Mountain View, Calif., 1937.*)

Recently several small volumes have been published dealing with the pathology of the nervous system; to these Courville's book is a splendid addition. As a basis for discussion and to give some idea of the relative incidence of nervous disease occurring in a general hospital, the statistical data on lesions of the brain and spinal cord in a series of 15,000 autopsies performed at the Los Angeles County Hospital have been included. The neuropathology is dealt with under the following headings: congenital abnormalities, diseases of the intracranial blood vessels, infectious diseases, effects of trauma, intoxications, diseases of unknown etiology and tumors.

The book is illustrated with 200 cuts of photographs and pen drawings which stand out well upon the enameled paper. The rather unusual drawings convey at a glance the general relationships of abnormalities of the brain, such as abscesses and tumors, to lesions in other portions of the body. They also illustrate well the effects of trauma. Courville is particularly interested in traumatic injuries and this chapter is the best in the book. It is correct and refreshing to find disseminated sclerosis listed under diseases of unknown etiology instead of being classified with infections or intoxications. The publishers should be given considerable credit for the attractive manner in which the book is produced.

O. R. L.

Modern Treatment and Formulary. By EDWARD A. MULLEN. 707 pp. $5.00. (*F. A. Davis Company, Philadelphia, 1936.*)

In his single volume of 707 pages, Dr. Mullen attempts to cover a large part of the therapy employed in general medicine and its specialties. He not only discusses the treatment of disease entities but also includes therapeutic outlines for many symptoms of disease; for example, to catarrh he devotes nine and a half pages in recommending treatment for gastric catarrh, nasal catarrh, catarrh of the gall ducts, of the intestinal and of the genito-urinary tracts. Six pages are given over to conjunctivitis. On the other hand, only a little over half a page is devoted to diabetic coma. Many prescriptions, often of liberal proportions, follow

the discussion of a particular ailment. In the way of specific therapy the book is generally quite vague. For example, one obtains a poor idea of the currently accepted methods of specific serum therapy from reading the section on the treatment of pneumococcus pneumonia.

The last third of the book contains tables of differential diagnoses, doses, weights and measures, emergencies, poisons and antidotes, and a list of 373 stock questions and answers in English, French, German, Italian and Spanish.

R. C. T.

Dextrose Therapy in Everyday Practice. By E. MARTIN. 451 pp. Illus. $3.00 (*Paul B. Hoeber, New York, 1937.*)

An excellent and comprehensive review of the clinical application of dextrose therapy. A brief review of the chemistry of dextrose and a more extended discussion of its physiological action preface eleven chapters devoted to a discussion of dextrose therapy employed in a wide variety of diseases and disorders. The chapters are arranged under convenient headings. An extensive bibliography is appended to each chapter. Particularly noteworthy are the frequent charts illustrating the glucose tolerance curves obtained under conditions known to modify the character of the curve. An excellent set of illustrations clearly demonstrates the usual methods of administering glucose solutions. The 2,000 references included in the bibliography and the extended description of the clinical value of dextrose therapy should make this volume useful to investigators in the field of carbohydrate metabolism as well as to general practitioners.

G. W. T.

Clinical Electrocardiography. By THOMAS LEWIS. 6th ed. 128 pp. Illus 8/6. *Shaw and Sons, London, 1937.*

A new edition of an introduction to electrocardiography which has served as a guide for beginners during the past twenty years. This small handbook represents a condensation of a larger treatise, *The Mechanism and Graphic Registration of the Heart Beat,* in which the author recorded the results of his fundamental experiments in the field of electrocardiography.

To the first edition of the work under review, there have been added a few pages dealing with the electrocardiographic changes following myocardial infarction; a brief note on the effect of quinidine in auricular fibrillation; and an implied concession that the original nomenclature of Bundle Branch Block, derived from an experimental study on dogs, may have to be revised. Otherwise, the original text has been retained almost verbatim.

Except for the absence of comment on the recent investigations with semi-direct leads from the chest wall or esophagus, the present work, despite its brevity, is singularly complete. Its excellence lies in the fundamental nature of the author's original research and in the concise, lucid style which characterizes this as well as his other publications.

R. F.

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6

PAROXYSMAL HYPERTENSION AND OTHER CLINICAL MANIFESTATIONS ASSOCIATED WITH BENIGN CHROMAFFIN CELL TUMORS (PHAEOCHROMOCYTOMATA)

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INTRODUCTION

In the past decade there has come into prominence a group of tumors composed of cells of adult chromaffin tissue, which under certain circumstances have given rise to a clinical picture sufficiently clear cut to be recognized. The surgical removal of these tumors, moreover, has been followed by complete alleviation of the distressing symptoms. Although the clinical syndrome with which we are here concerned is a relatively rare one, the surgical attempts in dealing with it have been so successful that it behooves us to make every effort to recognize the condition when we meet it. Such recognition is by no means easy, as we can attest, for one of the authors has seen in the past two years three patients in whom this condition may or may not have been present. The diagnostic problems of these patients led us to a more careful study of the literature in regard to this most interesting disorder and in order to acquaint ourselves better with the clinical picture of paroxysmal hypertension in individuals who have chromaffin tumors, the present study was undertaken.

SELECTION OF CASES FOR STUDY

Sudden and wide fluctuations in arterial blood pressure have been noted in association with various pathological states (1, 2, 3, 4, 5), but in only this one group—benign chromaffin tumors—is the condition readily accessible to either medical or surgical cure. In the medical literature may be found numerous case reports of patients suffering with adrenal medullary tumors, some with hypertension, often of a paroxysmal type, but the greater part of these case reports afford only the briefest clinical data and were felt to be unsuited to

our purpose, which is primarily to evolve a clinical picture that will be recognizable. For this reason we have sifted from this large number only those case reports in which not only adequate clinical histories and observations were made, but in which verification of the pathologic diagnosis was also obtained either at the operating table or at autopsy. Eighteen such cases have been collected for analysis; eleven of these patients were operated upon. In nine of these improvement was spectacular and, so far as we have been able to ascertain, permanent relief of the paroxysms has been achieved.[1] In the tenth case the tumor was not found at the operation and the patient died on the following day, presumably of a cerebral accident. In the eleventh case the patient went into a state of collapse during operation, and although there was temporary improvement with administration of intravenous glucose, he died of pulmonary edema just after the injection was finished.

As far as we are aware, the first clear cut description of the syndrome under discussion was published by Labbe, Tinel and Doumer in 1922 (6). The first report of an operative removal of such a tumor with relief of symptoms was made by C. H. Mayo in 1927 (7). The tumor was described in his article as a retroperitoneal malignant blastoma. After further cases with similar symptoms had been reported, however, the sections were reviewed and the diagnosis was changed to phaeochromocytoma (8). Actually, the first report of a successful operation for this type of tumor that we have found was published by Roux (9) in February, 1926. From the very brief description of the symptoms in his patient we feel quite sure that paroxysmal hypertension was present, but no blood pressure determinations are given. The combination of correct pre-operative diagnosis and successful surgical removal of a phaeochromocytoma with paroxysmal hypertension was first achieved by Pincoffs and Shipley (10, 11).

In the Pathological Department of the Johns Hopkins Hospital the records of only three patients with such tumors have been found. One of these three arrived at the hospital moribund and the clinical record available is too meagre to serve our purpose. The second is to be published separately as a case report by Drs. B. M. Baker and W. F.

[1] We are grateful to the authors who, at our request, obtained the latest follow-up reports on their patients.

Rienhoff (12), but we have their permission to use the clinical record of their patient in our summaries. The third we are reporting here for the first time. These last two cases together with 16 reports in the literature form a group of 18 patients whose symptomatology we have carefully studied and summarized. For the sake of the reader unfamiliar with the clinical syndrome under discussion we shall give the following brief record of our patient, whose history is fairly representative of the group as a whole. Abstracts of the other seventeen reports from the literature will be found at the end of the article.

CASE REPORT (NO. 17)

R. L. (J.H.H. U 19202, J.H.H. Path. No. 10457), a salesman of 69 years, was first seen in the Johns Hopkins Hospital on June 25, 1928. Little was known of his family history. In the past his general health had always been excellent. At 20 he had mumps and orchitis. He had been a heavy drinker of alcohol until 1916. In the early part of 1925 he began to have the attacks which were his chief complaint. At onset the attacks occurred about once every two or three months, but their incidence gradually increased to the point of one or even two daily. Between attacks he felt well but could not walk far because of dyspnea on exertion. The first attack occurred when he was quite excited and hurrying to make an important business deal. Usually, however, attacks occurred between 1 and 3 A.M., waking him from sleep. Attacks were always quite similar in character. Their onset was ushered in with two lusty sneezes, soon followed by a "sickening" pain in the epigastrium, radiating over the sternum and leaving some tenderness of the skin over the precordium and painful spots just above the internal condyle of each humerus. At the same time his neck would swell greatly, suggesting a goitre. During the attack dyspnea would be present and marked palpitation. Generally vomiting occurred, the vomitus consisting of small amounts of yellow material. After an attack he was generally drowsy for an hour or more, and he sometimes passed large quantities of urine during this period. The duration of each attack varied from a few moments to an hour. Additional symptoms noted during his three previous years were dysuria, frequency and nycturia (4–6 times); occasional tinnitus, and poor memory. There had been a loss of 25 pounds during the nine months prior to admission.

Physical Examination: Height 5 feet, 5 inches. Weight 145½ pounds. Temperature 98.6°. Pulse 80. Respirations 20. Blood pressure 138/84. There was some mental cloudiness. The skin showed evidence of recent weight loss. The retinal vessels were moderately sclerotic and the scar of an old hemorrhage was present in the right fundus. Dental caries and pyorrhea were present. The heart was slightly enlarged, and the lungs showed signs of moderate emphysema and chronic bronchitis. The peripheral arteries were tortuous and sclerosed. The liver was slightly enlarged. In the upper left quadrant of the abdomen

there was easily palpable a large, irregular, slightly tender mass, which moved with respirations. The left testis was atrophic. There was benign prostatic hypertrophy. Over the legs were a few varicose veins. The ankles pitted slightly on pressure. There was a marked coarse tremor of the extended fingers.

Urine: S. G. 1023; albumin, trace; sugar, negative. Microscopically there were 10–15 W.B.C. per high-power field, and an occasional hyaline cast.

Blood: Wassermann negative. Red blood cells 4.4 million; haemoglobin 83 per cent (Sahli); white blood cells 7,800; differential count normal. Nonprotein nitrogen content 52 mgs. per cent; uric acid 4.4 mgs. per cent; creatinine 1.8 mgs. per cent.

Electrocardiogram: Sinoauricular rhythm, rate 71, Tiii inverted, Piii conspicuously notched. Diagnosis: Normal sinus rhythm. Slight preponderance of levogram.

X-ray: Slightly enlarged heart and aorta; bronchitis. Large deformity on greater curvature of stomach, probably produced by a mass lying outside of the stomach.

Gastric analysis: Fasting, no fluid obtained; 35 minutes after test meal of 100 cc. 7 per cent alcohol, slightly bloody fluid was obtained; free HCl not present, total acid 6.

Stool: Negative.

Course in Hospital: Attacks continued to waken him at night, about 3 A.M. Nitroglycerine afforded no relief; amyl nitrite was on one occasion thought to help a little. Because the true explanation of the patient's symptoms was not suspected, there is unfortunately no record of any blood pressure determinations made while the patient was having the attacks of which he complained. While in the hospital they occurred only between 1 A.M. and 3 A.M., and observations of his appearance, pulse, etc. are lacking in the record. Very wide fluctuations in his blood pressure, however, were noted from time to time on the ward, without coincident statements of whether or not the patient was having symptoms when the determinations were made. For example, one morning at 11 A.M., when he was being seen by a medical consultant, the following note is recorded: "The blood pressure shows an astonishing variation; within a short period of observation the systolic pressure varied from 260 to 160, the diastolic from 120 to 90." The usual routine blood pressure observations were recorded in the history as 138/84, 112/70, 112/68.

On July 3, 1928, a cystoscopic examination was made, and 100 cc. of residual urine were found. The appearance of the bladder was typical of prostatic obstruction. On the morning of July 4th the patient was found comatose, a cold clammy sweat over all his body, bleeding from the rectum, pulse 110, temperature 100.2°, râles in both lungs, blood pressure 114/82, and the nonprotein nitrogen had risen to 135 mgs. per cent. The patient died on the morning of July 5th. Complete autopsy obtained.

Anatomical Diagnosis: Medullary chromaffin tumor of left adrenal. Moderate cardiac hypertrophy. Hypertrophy of bladder. Diphtheritic cystitis. Diph-

theritic colitis. Lobular pneumonia. Colloid nodules in thyroid. Emphysema. Cholelithiasis.

Description of the Tumor: The abdominal cavity is quite normal throughout save for a mass, about equal in size to a grapefruit, which originates in the left upper quadrant and extends medially as far as the midline. It displaces the stomach anteriorly and does not invade and is in no way attached to the intestine, stomach, spleen or kidney. When the viscera are removed it is seen that this mass probably has its origin in the adrenal of the left side, since this gland is missing and the stalk of the cystlike mass is attached to the tissue in the region where one normally finds the adrenal.

Dr. Frank Kindell's note reads in part as follows: "The large cystic tumor from the region of the left adrenal is in greater part destroyed through hemorrhage and cystic change in the central portion, leaving a peripheral layer of fairly well preserved tumor. The tumor is encapsulated.

"The sections show, in the margins of the cysts, much old blood and some reorganization with fibrous tissue and many phagocytic cells containing old blood pigment. There also is considerable calcification. None of the tumor is too well preserved, but it does show strands of cells, most of them rather elongated, others polygonal, and there is an occasional large cell with one or two nuclei or a single very large nucleus. The better preserved portions show an extremely delicate stroma with wide capillary spaces. In some areas the tumor cells have a slight yellowish coloration without definite granules. In still other places there is a definite brownish pigmentation showing a typical chrome reaction in the cells like those of the adrenal medulla.

"The opposite adrenal is normal. There is moderate cardiac hypertrophy (heart weight 420 grams). The microscopical preparations from the other organs show no arteriolosclerosis. There are sclerotic small vessels in the spleen, and two or three arterioles with early hyalin changes can be found in the pancreas. The kidney shows only a few scars and slight thickening of the vessels. No real glomerular or vascular alterations are seen." No studies of the adrenalin content of the tumor were made.

ANALYSIS OF EIGHTEEN CASES OF PHAEOCHROMOCYTOMA WITH PAROXYSMAL HYPERTENSION

Sex and Age: Of the eighteen patients, eight were females and ten males. The youngest was a male 16 years of age and the oldest a man aged 69. At the time the patients were studied their average age was 32.3 years. The age of the patients at the onset of symptoms was as follows: in the women 16, 23, 27, 28, 29, 29, 30 and 37, an average age of 27.5 years. In the men the ages at the onset of symptoms were 16, 20, 28, 29, 35, 36, 38, 40, 44 and 66, an average of 32 years. It

may therefore be said that in this group of patients the condition is essentially one of youth and early middle life.

Duration of Symptoms: This varied from eleven years to only a few months at the time studied. Long intervals of freedom from symptoms occurred in two patients, one of whom had an interval of four years when free from attacks (case 5), and the other patient had a period of six years of freedom from attacks (case 13).

Frequency of Attacks: The frequency of attacks was often reported to increase greatly as the duration of the disease progressed. Thirteen of the reports specifically stated this to be true. For example, in case 3 the attacks at the onset occurred only once in three weeks, whereas two years later they were occurring almost daily and sometimes several times daily. In case 10 the early attacks occurred at monthly intervals, whereas nine years later they had reached a frequency of an attack once a day. The usual report was that at onset they occurred two or three times a week and then steadily increased in frequency so that they occurred either once or several times daily.

Duration of each Attack: This varied widely; the longest attacks were reported in case 14, some of them lasting as long as sixteen hours. The average duration of attacks lay between one and two hours. In 5 cases the individual attacks were always short, being reported to last from 3 to 20 minutes.

Precipitation of Attacks: Certain definite factors were found to play a rôle in the precipitation of attacks in eight of the cases. Physical exertion induced attacks in 3 patients (Nos. 2, 3, 15). Nervous or emotional stress was followed by an attack in 3 patients (Nos. 3, 5, 15). In these three the tumor was located in the adrenal gland itself, but in seven other cases in which the tumor was also in the adrenal gland emotions did not seem to be a factor in the induction of attacks; *i.e.*, the induction did not seem to be under the usual nervous control mechanism. A most interesting association was found in 5 patients in whom an attack could be induced by bending into certain positions (Nos. 6, 7, 10, 12, 16). In case 6 assumption of a slight inclination forward and to the left would produce an attack. The tumor was in the right adrenal. In case 7 turning, or bending or lying on the left side would induce an attack. In this case the tumor was retroperitoneal in the left upper quadrant. In case 12 an attack was pro-

duced when the patient was placed on the operating table on the left side with the arm raised. This may have had to do with either the spinal anesthesia, as suggested by the author, or with the position assumed. The tumor was in the right adrenal in this patient. In case 10 simply bending is described as inducing an attack; the tumor was located in the right adrenal. In case 16 attacks were induced by bending the body over backwards and such acts as gargling. The tumor in this case was egg-sized in the right adrenal gland, adherent anteriorly to the under surface of the liver. It may be of significance that in all the patients in whom attacks were induced by bending into certain positions the tumor was of considerable size and, except for case 16, a palpable mass was present on the side on which the tumor was located. In two cases (nos. 10 and 13, in both of which there was also a large tumor) pressure on the upper abdominal quadrant, in which the tumor was situated, induced an attack; and in case 13 the terminal episode occurred soon after drinking a liter of water for a renal dilution test. In two cases (nos. 13 and 15) the attacks are described as worse with the menses, in another (no. 10) they are described as worse and more frequent just before the menses.

Time of Day at which Attacks Occurred: In 6 instances the most frequent time for an attack to occur was early in the morning. This was described in the individual cases as follows: (no. 1) "early morning on waking and also at irregular times"; (no. 2) "most often after breakfast"; (no. 8) "most frequently occurring in the morning"; (no. 10) "between 3 and 8 A.M. almost always"; (no. 9) "generally occurred between 9 and 10 A.M. and sometimes at 5 A.M., especially while making morning toilet"; (no. 12) "usually on first rising in the morning". In 4 cases the most prevalent time seemed to be while in bed at night; (no. 11) "generally occurred at night"; and (no. 6) "attacks at first occurred while in bed"; (no. 17) "attacks usually occurred between 1 and 3 A.M., waking him from sleep"; (no. 18) "occurred usually during the night". A relation to meals is mentioned in five cases; (no. 5) "often after meals"; (no. 2) "most often after breakfast"; (no. 13) "mostly in the daytime, especially after eating"; (no. 7) "usually one half hour after meals"; (no. 15) "after eating rich meals". There is no statement made as to the most probable time of occurrence of attacks in 5 cases.

General Health: In 11 cases the general health was described as either good or excellent. In 7 instances the patients were not in good health at the time of study. Patient no. 2 is described as having been run down for ten years; no. 5 is described as having had frequent diarrhea and vomiting; no. 7 was suffering from active pulmonary tuberculosis and pronounced symptoms of diabetes mellitus; no. 13 was very nervous and was thought to have had a nervous breakdown and hyperthyroidism; no. 4 had had a hemiplegia when first seen, and no. 16 had very severe hemorrhagic retinitis. Our patient (no. 17) felt quite comfortable between attacks except for dyspnea on exertion.

CLINICAL FINDINGS BETWEEN HYPERTENSIVE ATTACKS

General Appearance: Between attacks the general appearance seemed normal in most cases except in the patients who had the associated disturbances as mentioned above. Certain abnormal features, however, were remarked upon. The face was described as flushed, even between attacks, in 4 patients (nos. 1, 7, 8, 10). Exophthalmic goitre was suggested to the examiner in 3 cases; patient no. 1 showed tremors suggestive of Basedow's disease; no. 10 had an exophthalmic stare and case 13 had been mistaken for one of hyperthyroidism because of tachycardia and moist skin. An anxious expression was worn constantly by patient no. 15.

Pupils: Even at rest the pupils were described as widely dilated in three cases (nos. 1, 9, 10). The pupils were not mentioned in the other cases except in no. 13, in which they were described as small. In our patient (no. 17) the pupils were normal.

Fundi: Evidences of arterial changes in the optic fundi, such as sclerosis or hemorrhages were found in 7 cases (nos. 3, 11, 13, 14, 16, 17). In the rest the fundi were not mentioned or were described as normal. The 7 patients who showed the retinal changes were 69, 46, 45, 40, 38, 37 and 16 years old, respectively. Therefore 6 out of 7 of the patients in whom retinal changes were found were over 37 years of age, which is quite a bit above the average age of this group of 18 patients. One of the patients who showed retinal changes, however, was 16 years old; his retinal vessels showed improvement after operation. There is little correlation between the retinal changes and the duration of symptoms; for, although in cases 7 and 13 the symptoms

had been present for 9 and 11 years, respectively, four of the five patients with retinal changes had had symptoms for only eighteen months or less. Nor could the retinal changes be correlated with the height to which the blood pressure rose during attacks; for although in all these cases with retinal changes the blood pressure became very high, the rises were not higher than the average of the whole group, and others in the group with just as high blood pressure during crises showed no retinal changes whatever. One does find, however, that in all but one of the patients with retinal changes there was persistent hypertension, *i.e.*, even between paroxysmal episodes the resting blood pressure was above the levels which are generally considered to be normal. This single exception was our own patient (no. 17) whose palpable peripheral vessels were hard and tortuous, as might be expected from his age of 69 years. On the other hand one might point out that, although in 11 of the 18 cases there was persistent hypertension of some degree, only six of this group had eyeground changes, so that the correlation is not very close. Using the records of the 8 patients on whom autopsies were performed, Chart I has been drawn up to show the correlation between the status of the kidneys and the findings in the optic fundi, the resting blood pressure, and the duration of the disease.

Heart: Abnormalities on examination of the heart were found in 9 patients. In two (nos. 9 and 10) an accentuation of the second aortic sound was noted, and this was the only abnormal finding reported; in the former patient the resting blood pressure was elevated, in the latter not. In nos. 7, 16 and 17 the heart is simply described as enlarged. In two cases (nos. 4 and 12) a systolic murmur at the base was present without other abnormalities. In no. 13 the heart was slightly enlarged; a gallop rhythm was present, and both the second aortic and second pulmonic sounds were accentuated. In no. 11 a loud systolic murmur was everywhere audible, but the heart was reported to be normal by x-ray examination. In the other cases the examination of the heart was either normal or not mentioned. No myocardial failure was reported on the first observation of any patient except ours, in whom slight hepatic enlargement and slight pitting of the ankles were the only evidences of cardiac decompensation.

Pulse: The resting pulse was normal in eleven of the patients. Six

of the patients showed persistent tachycardia; five of these had pulse rates between 100 and 120, and on one it was described simply as tachycardia. Two authors commented on the marked lability of this tachycardia, as in case 1, for example, in which the pulse is reported to have risen from 100 to 130 on the slightest provocation.

CHART I

Observations made upon the eight patients who came to autopsy

CASE	KIDNEYS	HEART SIZE OR WEIGHT	OPTIC FUNDI	RESTING BLOOD PRESSURE	DURATION OF SYMPTOMS	SIZE OF TUMOR
1	No nephrosclerosis	340 grams	Normal	150/100	Several months	Tangerine
3	Normal	Enlarged	Hemorrhages. Arteriosclerotic changes	230/130	One year	7 x 6 x 5 cms.
4	Nephrosclerosis	350 grams	Normal	160/100	Ten to eleven years	Small orange
7	Mild nephrosclerosis	600 grams	Hemorrhages and arteriosclerotic changes in vessels	160/120	Nine years	Grapefruit.
12	Normal	Enlarged	Normal	170/80	Seven years	14½ x 8 x 6 cms.
13	Moderate nephrosclerosis	460 grams	Old and fresh hemorrhages. Arteriosclerotic changes	185/105	Eleven years	560 grams, 13 x 12 x 8.5 cms.
16	Grossly normal. Marked arteriolosclerosis	445 grams	Papilledema and marked exudates. Narrow arteries	203/158	Seventeen months	Egg size
17	Only a few scars. Slight thickening of the vessels	420 grams	Vessels moderately sclerotic. One old hemorrhage	112/70	Three years	Grapefruit

Blood Pressure: The resting blood pressure varied from perfectly normal to quite markedly elevated systolic and diastolic levels. In 11 of the 18 cases there was persistent hypertension (Chart II). In 4 of these patients (nos. 1, 3, 14, 16), who were followed over moderately long periods of time, the resting pressure changed from normal levels to persistent hypertension, though of course rising still further with the paroxysmal episodes. It has been suggested that in the early stages the blood pressure will always be found to be normal

when the patient is not having a paroxysmal attack; but if the disease lasts long enough, the pressure will eventually be permanently elevated. In the patients whose symptoms had endured the longest, however, seven years or more (nos. 4, 5, 7, 10, 13, 15), the resting blood pressure was normal in three of the six (nos. 5, 10, 15). Patient no. 14 showed, when first observed, a resting blood pressure of 140/80 and only a few months later was found to have a persistent

CHART II

Blood pressure observations in the eighteen cases

CASE	AGE	SEX	DURATION OF SYMPTOMS	RESTING BLOOD PRESSURE	BLOOD PRESSURE DURING ATTACKS
1	28	F	Several months	150/100	260/180
2	30	F	One and one half years	130/82	Exceeding 300/180
3	37	M	One year	140/80—210/130	Exceeding 300/180
4	29	M	Ten to eleven years	160/100	300/?
5	26	F	Ten years	120/90	260/120
6	39	M	Six months	110/?	Exceeding 200/?
7	46	M	Nine years	160/120	280/180
8	29	M	One and one half years	150/115	325/200
9	41	M	One and one half years	200/100	340/110
10	36	F	Nine years	120/80	300/240
11	16	M	Five months	125/105	300/200
12	45	F	Seven years	170/80	Exceeding 300/240
13	40	F	Eleven years	185/105	290/158
14	45	M	Seven months	140/90	Exceeding 260/120
15	37	F	Seven years	100-130/60-90	155-220/110-130
16	38	M	Seventeen months	145/?—200-225/145-160	330/120
17	69	M	Three years	112/70	260/120
18	27	F	Four years	120/80	240/180

hypertension of 210/130; patient no. 16, when his attacks began, had a resting systolic blood pressure of 145 which seventeen months later had risen to 225/160, thus showing that this change can take place very rapidly and need not necessarily occur in those patients who have had the syndrome the longest (see Chart II).

Electrocardiograms: Electrocardiograms were made in 9 cases. They were reported as normal in five. Our patient showed a levogram, Tiii inverted and Piii conspicuously notched. Case 13 showed a

levogram, very large P waves and sinus tachycardia. Case 11 showed a sinus tachycardia, inversion of T in leads one and two. In both cases, nos. 13 and 11, a persistent hypertension was present. Electrocardiograms were taken on 3 patients during the attacks, and results will be reported when the findings during attacks are described.

Detectability of Tumor: (A) *Abdominal Palpation.* A mass was palpable on the side in which the tumor was found in 8 of the 18 cases. In one of these (no. 7) a hard mass palpated in the left upper quadrant was mistaken for spleen; autopsy disclosed the tumor lying retroperitoneally in the left upper quadrant pushing the kidney down. In nos. 4, 8, 10, 12, 15 the palpable mass also proved in each instance to be the kidney, which had been pushed down by the tumor mass. In our patient (no. 17) the tumor mass itself was palpable. Although not reported as palpable prior to operation, in case 18 the liver was found at operation to have been pushed down to the level of the umbilicus by the tumor.

(B) *X-rays of Abdomen.* In 6 cases plain x-rays of the abdomen were taken; in three of these (one being the case in which the x-ray interpretation of an enlarged spleen proved incorrect) the location of the tumor was suggested by the plain abdominal plates.

(C) *Pyelograms.* Pyelograms were taken in 7 cases and definitely localized the tumor in 4 instances (nos. 8, 10, 12, 18). If pyelograms had been taken in the other eleven cases we feel from subsequent findings in regard to their sizes and locations that the tumors would in all probability have been localized in six of them (nos. 1, 4, 6, 7, 13, 15). Thus it is felt that in the present group of 18 cases, eleven of the tumors were definitely detectable by pyelographic study. Pyelograms failed to localize the tumor in 3 cases (nos. 11, 14, 16), and would almost certainly have failed in two more had they been made (nos. 2 and 9); also, judging from subsequent findings, it seems highly doubtful in our minds that the tumor's location in cases 3 and 5 could have been detected by this means.

Therefore it can be said that the location of the tumor could be strongly suspected by abdominal palpation in 8 cases; that its location was definitely detectable by radiographic means in 11, that it was not detectable in 5 and doubtfully so in 2 cases.

Blood Chemistry: Some of the chemical constituents of the blood

were determined in 11 patients between attacks. Fasting blood sugar was determined in all of these eleven, and was found to be normal in all except the patient who had frank diabetes. The blood nonprotein nitrogen, or urea, was reported in 12 patients, and in 4 was elevated at some stage of the disease. Of these 4 patients with elevated nonprotein nitrogen, in 3 there was a persistently elevated blood pressure, but it is perhaps worthy of note that in 5 of the 7 patients showing eyeground changes no elevation of the nonprotein nitrogen was present. Blood calcium was studied in only 3 cases, and was normal in all.

Blood Counts: In the cases for which figures were recorded there were no striking deviations from normal in hemoglobin or red blood cell count with the exception of case 2. This patient had been "run down" for ten years and showed rather marked secondary anemia. White blood counts and differential counts were all normal (where reported) except as follows: case 13 showed a white count of 23,000 and case 6 a white count of 14,000. Case 8 showed 4 per cent eosinophiles and case 6 a slight eosinophilia, around 3½ per cent.

Urine: The urine secreted between attacks was reported as normal in 9 cases. Intermittent albuminuria was present in 3 cases, apparently regardless of the attacks. Persistent albuminuria was found in 6 patients. Five of these six had persistent hypertension (Chart III). Glycosuria was present in one patient (no. 7) who had frank diabetes, and was not found between attacks in any of the others.[2]

Special Studies: Special studies were done and reported on nearly all the patients, but the nature of these studies varied very greatly. The Wassermann reaction was either negative or not reported in all. Gastric analysis was recorded in 4 cases, with normal results in all except for our patient, who had achlorhydria. Adrenalin tolerance tests were reported in 3 cases. In case 1 one milligram of adrenalin given subcutaneously produced a rise in blood pressure from 135 to 165 millimeters of mercury, without change in pulse and without palpitation. It did, however, produce glycosuria (blood determina-

[2] In case no. 18 glycosuria was observed late in the course of the disease on several occasions, but no statement is made as to whether the glycosuria occurred subsequently to, or during an attack. One might assume from other cases that this intermittent glycosuria was the direct result of paroxysmal hypertensive episodes.

tion not made) in this patient, which spontaneous attacks did not do. The blood sugar was not determined in spontaneous attacks in this patient and the urine during spontaneous attacks was suppressed. For case 5 the report is simply "Goetsch test—not hypersensitive". In case 11 the statement is simply made that the patient was hyposensitive to adrenalin as compared with Jensen's studies.

CHART III

Observations on the urine, optic fundi, and renal function of the ten cases who had persistent hypertension

CASE	AGE	RESTING BLOOD PRESSURE	URINE (NOT DURING AN ATTACK)	EYE-GROUNDS	KIDNEY FUNCTION
1	28	150/100	Albumin one plus or negative. Sugar negative	Normal	Not reported
3	37	210/130	Albumin and sugar negative	Arteriosclerotic changes	Not reported
4	29	160/100	Albumin 1–2 grams. Sugar negative	Normal	Not reported
7	46	160/120	Albumin negative. Sugar four plus	Arteriosclerotic changes	Phthalein normal
8	29	150/115	Albumin one plus. Sugar negative	Normal	Blood urea 52
11	16	125/105	Albumin one plus or negative. Sugar negative	Arteriosclerotic changes	Phthalein 52 per cent
12	45	170/80	Albumin one plus. Sugar negative	Normal	Normal
13	40	185/105	Albumin and sugar negative	Arteriosclerotic changes	Phthalein 75 per cent
14	45	140/90	Albumin and sugar negative	Arteriosclerotic changes	Phthalein 45 per cent
16	38	180–225/130–160	Albumin one plus. Sugar negative	Marked hemorrhages and exudates	Ambard 0.08

A test of sensitivity to pituitrin was reported in one case (no. 5) and the statement is made that the reaction to pituitrin was normal, with no further comment.

Sensitivity to hyperventilation was reported in only one patient, who spontaneously developed tetany during her hypertensive episodes. Five minutes of hyperventilation induced tetany in this patient and also induced a mild paroxysm of hypertension.

Basal metabolic rate determination was reported in 5 cases: in case 7, plus 23; in case 8 it varied from plus 10 to minus 14; case 9, "normal"; case 13, "elevated"; case 18, minus 14.

X-ray studies, other than those of kidneys and pyelograms were reported in a good many cases but showed no abnormalities other than cardiac enlargement as previously stated, except in case 7, in which the left diaphragm was reported "weak; question of slight eventration". In this case the tumor was in the left upper quadrant and may have had to do with this x-ray finding.

Oculo-cardiac reflex was tested in 2 cases. In case 1 pressure on the eyeball at first slowed the pulse from 100 to 56. Two months later the same procedure slowed the pulse from 112 to 108, and still later in the course of the disease the pulse rose during this procedure from 96 to 100. In case 9 this test was made only once and slowed the pulse from 80 to 66. In this patient a slowing of the pulse also occurred spontaneously during the hypertensive attacks. Epigastric pressure in case 9 also slowed the pulse from 80 to 66.

SYMPTOMS AND CLINICAL FINDINGS DURING HYPERTENSIVE ATTACKS

The first subjective symptom of an impending attack proved to be widely varied. *Palpitation* was the first symptom noted in 6 cases; nausea was the first to be noted in one case, and a peculiar sensation in the epigastrium similar to nausea in another. Peculiar sensations in the arms ushered in an attack in three cases, in one simply described as a "hot feeling in the arm", in another "a prickly sensation in the extremities, similar to cramps", and in the third "numb extremities"; tightness under the chest and pain of anginoid character in two cases; epigastric pain in one case; roaring in the head in one, occipital headache in one, and in another the first symptom was a sensation of heat around the face. Coincidently with the other sensations at the onset of attack one patient had cramplike pain in the back of the neck and another sometimes felt "a beating pulsation, like a pulse in the eye". Two lusty sneezes invariably ushered in attacks in one patient.

Pain: In 15 of the 18 patients, severe pain in one area or another invariably accompanied an attack. Two were described as precordial only. Epigastric pain occurred in seven. In one case epigastric pain radiated to the head and neck. In another case the pain began with cramps in the legs, then moved to the abdomen, then

became precordial and later a terrific headache, though in any individual attack only one of these areas might be affected. Pain is described in the fingers and toes in one case, in the back of the neck in one case, as a pressure in the head in one case, as a "severe binding headache" in one, and as lower abdominal and lumbar pain in still another.

Precordial Pain: At the height of an attack precordial pain which could be described as anginoid in character occurred in 8 cases, or 44 per cent.

Headache: Headache is described in 10 cases. The headache is variously described as "severe occipital" in 3 cases; "as if it [the head] were going to burst" in one case; "sense of pressure on top of the head and vertical headache" in one case; and in another the headache is described as "following the attack and very severe"; "severe and binding" in another. In 7 patients it was either specifically stated not to have occurred or was not mentioned.

Vomiting: During attacks spontaneous vomiting occurred in 13 cases. In one case (no. 14) there was nausea without vomiting and in two cases nausea was present so that the patient would induce vomiting with some relief. Nausea was therefore present in 16 of the 18 cases or 88 per cent. The vomiting was described in various ways, for example, "severe during whole attack"; "severe". In several of the cases it was noted that vomiting occurred in some, though not all, attacks.

Respirations: In 4 cases respiration was reported to be elevated in each attack. In case 5 the respirations rose to 36 per minute, and dyspnea was present. In case 10 respirations are simply described as rapid. In cases 11 and 17 the patient was described as being dyspneic but the respiratory rate was not mentioned. In case 14 "breathing is difficult, up to 30 per minute". Pulmonary edema occurred in one or more attacks in 9 cases (nos. 1, 2, 3, 4, 8, 11, 12, 13 and 18). Three of these patients (nos. 4, 12 and 13) died in their first attack of pulmonary edema.

Palpitation: Palpitation, or objective vigorous action of the heart, was described in all but one case during the attacks, *i.e.* in 94 per cent. In this one case (no. 11) palpitation is not mentioned. The heart action is variously described, but in most cases must have been very

vigorous; for example "whole body shook"; "shook bed and chair"; "as if head would burst".

Sweating: Sweating is described in 14 cases, or 78 per cent. It occurred at the end of an attack in 6 cases; during the attack in 6 cases. The time of the occurrence of sweating in relation to an attack is not reported in one case and in another it is reported as occurring in waves coincident with the fall in blood pressure at three to five minute intervals, *i.e.* sweating occurred when the pressure was in the remittent phase.

Pilomotor Phenomena: It is most regrettable that the presence or absence of pilomotor phenomena was not mentioned in any of the cases.

Vasomotor Phenomena: In 9 cases the face is described as becoming very pallid; purplish mottling or ashen cyanosis is described in 7 cases. In 2 cases (nos. 10 and 18) there was blanching and flushing intermittently coincident with the rise and fall, respectively, of the blood pressure. In cases 12 and 16 the face is described as "pale at the onset of the attack but followed soon by flushing". In addition to the color changes, one patient is described as having a "mournful expression" during attacks and another as being "pale but with rosy ears and tongue slightly cyanotic". In two cases the face is reported as cold to the touch, but in view of the very marked pallor reported, the face probably felt cold in all cases even through it was not so noted. The extremities were described as being cold during the attacks in all instances except in our patient, and no mention is made in the record of any observations of his extremities. In 14 cases this was associated with marked pallor; in 2 cases (nos. 5 and 7) the extremities were described as cold and mottled in appearance.

Neck Veins: A remarkable distention of the neck veins is described as occurring in five of the cases and in one of these (no. 9) actual measurements before and during an attack showed an increase of 3 cm. in "cervical circumference." In our patient the neck swelled so greatly, according to the patient's wife, that "it resembles a goitre" and "the swelling disappears as rapidly as it comes".

Tetany: Tetany occurred in only one case (no. 10). In this patient vomiting was a very prominent feature of the attack, as was also hyperventilation. The fasting blood calcium in this patient was 10

mgs. per cent, so that the tetany may therefore be considered as probably alkalotic in origin.

Convulsions: Convulsions were not described in any of the patients in this group.

Chills: Chills were not described in any of the cases.

Fever: Fever was not described during the attacks in any of the cases except nos. 12 and 17 in which the temperature rose to 107° and 104° in the terminal episode.

Blood Pressure: The blood pressure, of course, rose paroxysmally in all patients of this series (see Chart II) but is described in a great variety of ways. Because the description in no two cases is identical, it seems wisest to quote from each case report. Case 1, "elevated during attacks, diastolic up correspondingly but both may be high even without subjective evidence of attacks. Typical attack 260/180"; no. 2, "markedly elevated—300/180", blood pressure rose before the pulse; no. 3, "over 300/180"; no. 4, "systolic up to 250–300", diastolic not stated; no. 5, "190/98 rising to 260/120 in attacks"; no. 6, "within 90 seconds of first sensation blood pressure rose from 110 to 200 or more"; no. 7, "280/180 immediately after onset, ten minutes later 250/150, 30 minutes later 120/98", which is lower than the average resting blood pressure (160/120); no. 8, "325/200, returning to normal in one half hour"; no. 9, "340/110"; no. 10, "300/240, down to 90/60 at three to four minute intervals associated with marked change in the symptoms"; no. 11, early in the course of the disease "300/200 falling to 150/115 at five minute intervals;" later in the course of the disease this curious fluctuation during attacks was not manifest; no. 12, "over 300/240"; no. 13, "290/185"; no. 14, "260 or above/150"; no. 15, "155 to 220 systolic and 110 to 130 diastolic"; no. 16, "average 185/120 to 330/120". In the patient we are reporting (no. 17) it is regrettable that the blood pressure was not taken during a symptomatic attack, but even without symptoms it was noted on occasion to go as high as 260/120, whereas usually it was found to be low normal. Case 18, "blood pressure would rise to 240/180, gradually falling to 65/40 in waves, about fifteen minutes being the usual time between cycles".

As noted above, three of the cases showed remarkable wavelike variations in the blood pressure during the individual attacks. In

case 10 during an attack the blood pressure would rise to very high levels (300/240) for about five minutes and then fall rapidly to 90/60 for about five minutes, the cycle then repeating itself over and over during the whole episode, which might last from three to six hours. In case 18 there occurred wavelike fluctuations in the blood pressure during attacks of exactly similar nature, with rises to 280/160 and falls to 65/40 at approximately fifteen minute intervals. Somewhat but not exactly similar fluctuations were noted in case 11. Here, in the early part of the illness, the blood pressure during an attack would vary from 300/200 to 150/115 at approximately five minute intervals. In this third patient objective changes other than the fluctuation in the blood pressure were not noted, whereas in the former two patients rapid changes from marked blanching to flushing with sweating accompanied the blood pressure variations.

Pulse: During attacks the pulse was described as accelerated in 7 cases. It did not change from the resting rate in 4 cases. It was actually slowed during attacks in 4 cases. This slowing was described in case 6 as "down to 55"; in case 9 "from 84 to 72"; and in cases 11 and 18 slowing of the pulse accompanied hypertensive phases. In case 15 it apparently rose during some attacks and was slowed in others; whereas in case 16 early in the course bradycardia accompanied the hypertensive episodes, but later the pulse was accelerated during attacks.

Other Physical Findings: The pupils were reported to be markedly dilated during the attacks in 4 cases. An anxious expression was described in 3 cases. The heart was reported enlarged upon physical examination during or at the end of an attack in 2 cases (examination of the heart in these patients at other times showed no physical abnormalities), and was reported to be unchanged in one case. An electrocardiogram was taken during an attack in three patients (nos. 5, 15, 18). The record in case 5 showed very high T waves as in hyperthyroidism, irregularities at the end of attacks which consisted of short runs of auricular tachycardia, ventricular extrasystoles and ventricular tachycardia. In case 15 a diphasic T wave was observed in derivation I. In case 18 changes were found due to shift of the pacemaker from the S-A node to the lower part of the auricle or to the A-V node itself. These changes were such as might be expected

as the result of an overdose of epinephrine. One can say then that the electrocardiographic changes found during attacks on these patients were variable; in no case were they of significant assistance in establishing the diagnosis.[3]

In one case (no. 6) the capillaries of the nailbeds were studied and were found to be obliterated during an attack. In case 8 the patient felt hungry during some of the attacks and if not fed promptly, sweated profusely; (this is one of the cases in which no blood chemistry findings were reported either before or during an attack, and the urine after the attack showed albumin but no sugar). Actual body tremors during attacks were reported in 3 cases. Dizziness was reported during attacks in 2 cases, and marked salivation and watering of the eyes in 1 case (no. 3). Frequent swallowing during attacks occurred in case 15.

Blood Chemistry: Unfortunately the blood chemistry was studied during attacks of hypertension in only 6 cases. In case 10 only a very mild attack was studied and the only determination done at this time was of the blood sugar, which showed no change from the usual fasting level. Case 11 is also reported to have shown no elevation of blood sugar, although nonprotein nitrogen rose to 40 milligrams per cent in an attack. Most elaborate studies during the hypertensive crises were made in case 9, with the finding that the blood sugar paralleled the blood pressure, *i.e.*, before the attack it was 124 mgm. per cent, rising quickly to 224 mgm. per cent at the "debut" of the crisis, in 25 minutes was found to be 218 mgm. per cent, and one half hour after the crisis was over had fallen to 102 mgm. per cent. In this same patient the total serum protein rose slightly during the crisis and fell promptly afterward, probably showing slight concentration of the blood. The blood calcium rose slightly also, probably in association with the protein rise. The blood cholesterol showed no change. In the 6 cases studied the blood sugar rose during attacks in three, was very slightly elevated in one, and in two was found to be normal, although in one of these two in which the blood sugar showed no rise the report states that only a mild attack was studied. Nonprotein nitrogen was studied in only two cases during an attack; in one case

[3] Andrus, E. C.: Personal communication.

no change was found and in the other it rose slightly to 40 milligrams per cent.

Urine: Examination of the urine secreted during or soon after an attack was reported in 10 cases. Of these ten, glycosuria occurred in only four. It is of interest perhaps that three of these cases are the same in which blood chemistry studies were made during an attack and hyperglycemia was found to be present. Albumin either appeared during, or was increased after, an attack in 5 cases. The sugar and the albumin did not necessarily occur together, in fact did so in only one case (no. 9), and in this case albumin was persistent and was spoken of as increased after an attack. Suppression of the urine during attacks occurred in 2 cases (nos. 1 and 12).

Symptoms Following Attacks: Extreme fatigue and prostration were reported in 10 cases. Duration of this fatigue and prostration varied from a whole day to only a few minutes. Abdominal pain following attacks was reported in one case, and this was on the right side. Since the tumor later proved to be on the left side in this patient, it would seem likely that the rightsided pain was due to acute hepatic congestion. Constant lassitude from the onset of the illness was reported in two cases.

Relief or Alteration of Attacks: In two cases the first hospital visit itself seemed to alleviate the frequency and intensity of the attacks, and in one case similar improvement accompanied a vacation at the seashore. In one case (no. 3) x-ray to the adrenals was believed to have been the factor that relieved the patient of attacks for some months, but later on the attacks recurred, and the patient came to autopsy as the direct result of one of them. This case had previously been reported as a cure due to x-ray therapy (13). X-ray was given to one other patient (no. 7) with no benefit whatever. In cases 10 and 15 the attacks were completely absent during the whole course of a pregnancy, and again in case 10 during several weeks of a febrile episode which was thought to be due to a pyelitis. A wide variety of drugs was given during the attacks in attempts to alleviate the symptoms. In three cases amyl nitrite, and in one case morphine, was thought to help a little, but in other cases no change whatever was found in the character of the attacks as the result of the following drugs: digitalis, quinidine, bromides, chloral, luminal, belladonna,

potassium iodide, morphine, typhoid vaccine, histamine, choline, ergotamine, insulin, and nitroglycerine.

OPERATIONS

Eleven of the eighteen patients came to operation and all but two survived the procedure. Symptoms were entirely alleviated at the time the case report was made in the nine who survived. Three of the patients are known to be in excellent health and entirely free from attacks for as long a period as three, six, and eight years after operation (nos. 8, 5m and 2, respectively). Severe reactions to the operative procedure occurred in six cases; *i.e.*, as soon as the tumor was removed the blood pressure fell and the manifestations of shock became very prominent. The duration of shock varied: in case 5 it lasted for two days, in case 6 for one day; in case 8 for five hours; in case 11 only until transfusion could be given and then he was soon "all right"; in case 14 there was marked shock during the progress of the operation, improving slowly over the course of the next twenty-four hours; in case 18 shock came on as soon as the anesthetic was begun, and the patient died soon after operation. No shock whatever occurred during, or subsequent to, the operation in 4 cases. For the postoperative shock adrenalin was used, as well as the usual other measures that serve to counteract surgical shock, such as intravenous saline and transfusion. Pulmonary infarction occurred during the postoperative course in two cases. The blood pressure was normal at the time of discharge in all. The first of the two operative failures occurred because the tumor was not found at operation (case 16). The right adrenal felt normal in size to the operator, and since the left seemed enlarged the latter was removed. The blood pressure remained essentially unchanged postoperatively. On the following day the patient gave a sudden cry and died. Autopsy disclosed an egg-sized tumor in the right adrenal. The hypertrophy of the left adrenal was cortical in origin and the author (Volhard) logically assumes this cortical hyperplasia to have been compensatory for the cortical atrophy caused by the pressure of the medullary tumor of the opposite side. In the second operative failure the patient went into a state of collapse soon after the anesthetic was begun. The operation was continued and the tumor was removed. After operation intra-

venous glucose seemed to be bringing about marked improvement in the patient's condition, but immediately after the injection was completed pulmonary edema supervened, and he died.

AUTOPSIES

Eight of the patients died and were autopsied. Death was due in five of these to pulmonary edema. In one case (No. 3) death was attributed to uremia, although it is probable that just before death a crisis occurred, because the patient was said to have suddenly become very pale all over. In our opinion in case 16 death was probably due to a vascular accident. In the autopsied cases the heart weight was reported as follows: No. 1, "340 grams"; No. 4, "350 grams"; No. 7, "600 grams"; No. 13, "460 grams"; No. 16, "445 grams"; No. 17, "420 grams." In cases 3 and 12 the heart weight was not given but the heart was described as enlarged. The kidneys were reported as follows: No. 1, "normal, no nephrosclerosis"; No. 3, "normal"; No 4, "nephrosclerosis"; No. 7, "mild nephrosclerosis"; No. 12, "normal except for the compression caused by the tumor"; No. 13, "grossly, normal, microscopically, moderate arteriosclerosis"; No. 16, "normal size, a few scars, cortex of normal thickness, glomeruli essentially normal, arterioles show very thick but often completely homogeneous hyalinized wall"; No. 17, "normal save for a few scars and slight thickening of the vessels."

In all of the autopsied cases except ours persistent hypertension had been present during life. Three, however, showed absolutely no nephrosclerosis, and two showed only a mild degree of nephrosclerosis (No. 13 being grossly normal) (See Chart II). Autopsied patients of this series, despite persistent hypertension, show that nephrosclerosis was uncommon and when present was of mild degree except in one case in which it was marked. In another case the degree of nephrosclerosis was not stated. Nor did the retinal changes correlate with the degree of nephrosclerosis, for of the five patients who had retinal hemorrhages, one had marked arteriolar changes in the kidneys, two had mild nephrosclerosis, and the other two had normal kidneys (see Chart I).

PATHOLOGY OF THE TUMORS

Size of the Tumor: In the 18 cases the size of the tumor was reported as follows: No. 1, "the size of a tangerine"; No. 2, "6 x 4 cm."; No 3, "7 x 6 x 5 cm."; No. 4, "size of a grapefruit"; No. 5, "150 grams"; No. 6, "size of a kidney"; No. 7 "size of an orange"; No. 8, "size of a fist"; No. 9, "size of a cherry"; No. 10, "size of a fist"; No. 11, "8 cm. in diameter"; No. 12, "14½ x 8 x 6 cm."; No. 13, "weight 560 grams, measured 13 x 12 x 8½ cm."; No. 14, "size of an English walnut, weight 28½ grams, 4½ x 4 x 3½ cm."; No. 15, "240 grams, 10.5 cm. in diameter"; No. 16, "size of an egg"; No. 17, "size of a grapefruit"; No. 18, "10 cm. in diameter" (See Chart IV). The size of the tumor seemed to bear no relation whatever either to the number or the intensity of the attacks, but it must be noted that large areas in many of the tumors showed necrosis, hemorrhage, or cystic degeneration;

so that it cannot be said that there was no relation between the severity of the symptoms and the amount of actively secreting chromaffin tissue.

Location of the Tumors: The tumor was found to be situated in the adrenal gland itself in 13 cases (Nos. 1, 3, 4, 5, 6, 8, 10, 12, 13, 15, 16, 17 and 18). Of these 13, 3 were in the left adrenal and 10 in the right adrenal. In 5 of the cases tumors were not located in the adrenal gland proper. In these cases the location was as follows: In No. 2 mesial to the left kidney and behind the tail of the pancreas; No. 7 retroperitoneally in the left upper quadrant pushing the kidney down and

CHART IV

Size and location of tumors

CASE	LOCATION OF THE TUMOR	SIZE OF THE TUMOR
1	Left adrenal gland	Size of a tangerine
2	Mesial to the left kidney and behind the tail of the pancreas	6 x 4 cms.
3	Right adrenal gland	7 x 6 x 5 cms.
4	Right adrenal gland	Size of an orange
5	Just above right kidney	150 grams
6	Right adrenal gland	Size of a kidney
7	Retroperitoneally in the left upper quadrant pushing the kidney down and attached by a pedicle in the midline	Size of a grapefruit
8	Right adrenal gland	Size of a fist
9	Between vertebral column and aorta	Size of a cherry
10	Right adrenal gland	Size of a fist
11	Lateral and above hepatic flexure of the colon	8 cms. in diameter
12	Right adrenal gland	14½ x 8 x 6 cms.
13	Left adrenal gland	560 grams 13 x 12 x 8½ cms.
14	To the right of aorta, between the aorta and inferior vena cava	Size of English walnut 28½ grams 4½ x 4 x 3½ cms.
15	Right adrenal	240 grams 10.5 cms. in diameter
16	Within right adrenal, adherent anteriorly to under surface of liver	Egg-sized
17	Left adrenal gland	Size of a grapefruit
18	Right adrenal gland	9 cms. in diameter

attached by a pedicle to the midline, the adrenal lay just adjacent to it and was small; No. 9, the smallest of all the tumors, was found between the vertebral column and aorta, entirely independent of the suprarenal gland; No. 11, the tumor was lateral and superior to the hepatic flexure of the colon; No. 14, lay to the right of the aorta, between the aorta and inferior vena cava.

HISTOPATHOLOGY OF THE TUMORS

More or less detailed descriptions of the histopathology of the phaeochromocytomata, or benign chromaffin cell tumors, are given in conjunction with the various

case reports. These descriptions correspond very closely one with the other. Rabin (14) has presented a composite histological picture, based upon a review of thirty cases from the literature and one case of his own. More recently Eisenberg and Wallerstein, (15) and Lewis and Geschickter (16) have discussed the histopathology of these tumors at some length.

The tumors are always well encapsulated; in some cases the presence of normal medulla, separated from the tumor by a capsule, has been demonstrated, thus ruling out the possibility of simple medullary hyperplasia. Hemorrhages are frequently present, and necrosis and cyst formation are common features. The tumor proper consists of nests or cords of polyhedral cells separated by a thin connective tissue stroma, rich in capillaries, giving either an alveolar or a trabecular appearance. There is great variation in the size and shape of the epithelial cells with cuboidal and polyhedral cells of moderate size predominating; these cells are usually larger than those of the normal suprarenal medulla. A syncytial appearance is not uncommon. The nuclei vary as much as the cells in size; they tend to be rather large and contain a chromatin network which stains more deeply than that of the vesicular nucleus seen in the normal medulla. The nuclei contain one or more nucleoli. Multinucleated cells are often found in large numbers. The cytoplasm is finely granular; sections of the tumor fixed in bichromate solutions show brown pigmented granules or diffuse brown pigmentation in many, but by no means in all, of the epithelial cells. Thus the chromaffin cells are scattered among similar cells which take the brown stain poorly or not at all. Hyaline inclusions are present within the cytoplasm of the cells in most cases; these are much larger than the inclusion seen in the cells of the normal medulla. Since the inclusions fail to give the histochemical reactions of adrenaline, they are regarded as representing an intermediary phase of the secretion of adrenaline.

The majority of authors make no mention of the innervation of the tumors. Hick (17), however, describes what he considers to be sympathetic ganglion cells in and about the capsule of the tumor that he studied. To quote from his description: "Here were found cells which were somewhat different from those of the main tumor. They were oval or elongated, the nucleus was more vesicular, with a pronounced nucleolus, and many of the cells resembled sympathetic ganglion cells, although they were not surrounded by a distinct capsule. Many of the cells extended into branched processes which fused with the finely fibrillar intercellular substance. These fibrils, which were often arranged in bundles, stained purple-pink with Mallory's aniline blue method and could be easily distinguished from the bright sky blue connective tissue. These cellular accumulations were occasionally arranged about an artery and a vein flanked by bundles of nonmyelinated nerve fibrils."

Peyron (18) has compared the pathological picture of human paragangliomas (benign chromaffin cell tumors) with that of similar tumors occurring in domestic animals, such as the horse, the cow and the sheep. Certain structural features stand out much more sharply in the sections of the animal tumors, especially in the horse paraganglioma. Reasoning by analogy, Peyron feels that he is able better to explain the finer structure and the histophysiology of the human para-

ganglioma. He attaches particular importance to the presence of intra-epithelial cavities secondarily invaded by blood—a fundamental characteristic of the paraganglioma. These cavities at times present an angiomatous appearance when their walls are thinned out and compressed. In the horse paraganglioma the curious polarization of the nuclei of the epithelial cells in the pole opposite to the vascular endothelium lining these cavities furnishes strong evidence for secretion directly into these vascular channels. Such polarization of the nuclei is never a very prominent feature of the human tumors. On the basis of this observations on horse paragangliomas, however, Peyron interprets the intra-epithelium cavities in all types of paraganglioma as corresponding to the axial lacunae described by Lydia Felicine in the normal suprarenal medulla. He also finds the horse tumor most suitable for the study of the variations in the size, shape and staining properties of the vacuoles, inclusions and granules, which he believes are intimately related to the various phases of secretion and excretion.

Thus the histopathology of the phaeochromocytomata furnishes additional evidence that these tumors secrete adrenaline or adrenaline-like substances into the blood stream much in the manner of the normal suprarenal medulla.

EPINEPHRINE CONTENT OF THE TUMORS

Eight of the tumors in this group were studied in regard to their content of epinephrine. Biological methods of assay, however, were used in only five of these. The tests were made in most instances by analysing representative areas of the tumors, and calculating from such a sample the approximate total epinephrine content. Since most of the tumors were far from uniform in consistency, and since they nearly all contained many cysts and necrotic areas, it can be readily seen that the figures given are only the roughest sort of approximations. Allowing for these inaccuracies, cases 4, 10, 14 and 15 were found to contain 300 mgs., 375 mgs., 285 mgs. and 240 mgs. of epinephrine, respectively. Worthy of especial note is the fact that in case 15 the epinephrine was recovered from the tumor in crystalline form. The tumor of case 13 was studied by Dr. E. M. K. Geiling and was found to contain but 6.7 milligrams of epinephrine, and thus despite its large size yielded only a little more than the average amount obtained from a normal adrenal gland. According to Grollman (19) the average amount of epinephrine recoverable from both adrenal glands in the human is about 8 mgs.

DISCUSSION

It seems obvious that the cause of the syndrome with which we are concerned is the phaeochromocytoma. Most authors on the subject have assumed that the individual episodes, of which paroxysmal hypertension is the most conspicuous feature, are due to sudden massive discharges of epinephrine by the tumors into the general circulation. The available evidence seems to us to support strongly this assumption. There has been extracted from all the tumors in this

series which were so investigated a substance that showed all the biological characteristics of epinephrine, and with one exception the amounts obtained were very large indeed. The outstanding and most uniform symptoms and signs of the hypertensive episodes are quite analogous to those one might anticipate if a large dose of epinephrine were injected into the blood stream. Certain features, however, do not appear readily explicable in this way. For example, why did not the blood sugar rise in every instance during paroxysms and why did not coincident glycosuria occur? Glycogenolysis is one of the most characteristic responses to epinephrine injection, and yet from the foregoing case reports we must conclude that such glycogenolysis did not occur to any marked degree in all these cases, and perhaps did not occur in most of them. We shall have to leave this question for the pharmacologist and the physiologist to answer.

Another feature of great interest was the wavelike variations in symptoms and signs which occurred during individual attacks in two of the patients. In one patient the cycle from what appeared to be marked "epinephrinism" to the opposite state occurred every five minutes, and in the other approximately every fifteen minutes. It seemed in these patients as if there were rhythmical discharges of epinephrine that would reach a certain peak only to be followed by great discharges of stimuli acting in an exactly opposite direction. Perhaps the carotid sinus mechanism may have been responsible in these patients for this phenomenon, for Weiss (20) has shown that in different groups of human subjects there occur marked variations in response to carotid sinus stimulation.

Paroxysms of hypertension have been reported in association with pathological states other than phaeochromocytomata. It has been suggested that we shall be unable clinically to diagnose phaeochromocytomata with any degree of certainty until some reliable test is discovered for determining accurately the amount of epinephrine in the circulating blood at a given time, namely, during attacks. To the authors it seems that such a test, if discovered, would be of but little service in this distinction, for any pathologic state that would be seriously confused with a phaeochromocytoma and paroxysmal hypertension would be accompanied by massive discharges of sympathetic stimuli with inevitably associated adrenal medullary secretion.

From the large number of pathologic reports of tumors arising from

sympathetic nerve tissue, and from the comparative rarity of the clinical syndrome under discussion it is obvious that not all tumors of sympathetic origin produce paroxysmal hypertension. For example, in Geschickter's (21) large group of carotid body tumors there was nothing suggestive of paroxysmal hypertension in any of the clinical records. Most tumors of this origin not in the adrenal proper apparently arise in paraganglions. One might suppose that only tumors composed of highly differentiated cells would be capable of producing epinephrine, thus bringing about paroxysms of hypertension, but characteristic paroxysmal hypertension was manifested by a young

CHART V

Frequency of the occurrence of the principal symptoms of the eighteen cases during paroxysmal hypertension

SYMPTOMS	NUMBER OF CASES
Blanched or mottled cold extremities	17
Palpitation	17
Nausea	16
Sweating	14
Vomiting	13
Headache	10
Pulmonary edema	9
Precordial pain	8
Distention of neck veins	5
Dilated pupils	4
Body tremors	3
Dizziness	2

Belgian patient whose malignant tumor was composed of undifferentiated cells (22).

Of great interest also is the long interval of complete symptomatic freedom which may occur in these cases, one patient having no attacks for six years, and another being symptom-free for four years. We have no explanation for this curious feature, nor for the fact that pregnancy in some patients accentuated the attacks, while in others it was coincident with complete absence of attacks for its duration.

CONCLUSIONS

From this study of proven cases we feel that a fairly definite clinical picture emerges by which may be evaluated the possibility or proba-

bility of the presence of a phaeochromocytoma in a suspected patient. The individual most likely to have a phaeochromocytoma will be one of youthful or early middle age, of either sex and in good general health. The attacks of hypertension may vary widely in duration from a few minutes to many hours. There will generally be no known predisposing cause initiating the attacks, although the assumption of certain positions sometimes has been observed to induce attacks, and exertion and emotional stress have been felt by some patients to be precipitating factors. The attacks are more likely to come after retiring at night, and especially in the early morning hours. The patient will probably look and feel perfectly well when not actually having an episode of hypertension, although persistent hypertension is too common in this group to be totally ignored as part of the syndrome. Should persistent hypertension exist, the same manifestations will be found in the retinal arteries, heart examination and urinalysis as are commonly seen in patients suffering with so-called "essential hypertension". Electrocardiographic findings will be of no help in the differential diagnosis, even during a hypertensive attack. A mass in the abdomen, on the side of the tumor, may or may not be palpable on physical examination; there is greater possibility of its being found either by flat x-ray plates of the abdomen or by pyelographic studies, but the correctness of the diagnosis should not be seriously questioned if no mass is detected by any of these means. After paroxysms of hypertension albumin or sugar, or both, may possibly appear in the urine. Nothing in the way of medication has been found to influence materially the frequency, duration or severity of the attacks. If tests are made with epinephrine or pituitrin there will probably be found no hyper- nor hypo-sensitivity. During the early part of an attack (associated with the rise in blood pressure) the patient will almost certainly become cold, pale or mottled, and complain of palpitation. Quite pronounced nausea, and probably vomiting, is almost certain to be present and if of long duration, especially if accompanied by hyperventilation, may lead to tetany. Very severe headache is more apt than not to be complained of. If the attack is severe or prolonged, signs of cardiac incompetence are to be looked for, such as pulmonary edema, sudden hepatic enlargement or distended neck veins. Precordial pain with radiation to neck, down arms, or other areas characteristic of stenocardiac attacks

are quite likely to be present. Very pronounced sweating is apt to occur either during or just after the severe episode has passed. Even without any of the symptoms listed above, the patient whose usual resting blood pressure is normal may at any time be found to have quite marked temporary hypertension. In other words, milder paroxyms of hypertension may occur without the patient's being aware of them at all, just as is observed so frequently in the early stages of so-called "essential hypertension". It is perhaps worthy of emphasis, however, that in patients suffering from essential hypertension the course may be totally asymptomatic for a long period of time, whereas in this group of patients the symptoms are of sufficient severity early in the course of the disease to bring the patient to the doctor.

ADDENDUM

The authors deeply regret that it was not until after completion of this manuscript that their attention was directed to the excellent article on the same subject by Van Goidsenhoven and Appelmans. Their article was published in the *Bulletin de l'Academie Royale de Belgique in 1934*. In it they reviewed briefly the previously reported operative cases and reported in great detail a new case of their own in which the tumor was successfully removed with complete cure. In addition to the paroxysms of hypertension, their patient, a woman of 35, showed the following interesting features: constitutional symptoms that were quite marked, with weight loss and great asthenia; the presence of albumin in the urine after hypertensive attacks, but no sugar, despite the fact that administration of only 50 grams of glucose for a tolerance test provoked glycosuria; the development of episodes of "shock" during the latter part of the patient's illness prior to operation, these episodes sometimes lasting from two to three days, and being of such severity that diagnoses of internal hemorrhage and adrenal insufficiency were seriously considered.

APPENDIX

Case Abstracts

Case 1 (Labbe, Tinel and Doumer (6), 1922). A married woman of 28 years who had had a normal child three years before. She had been having symptoms for several months when first seen. The general health was excellent. Attacks occurred at first from three to four times weekly and later nearly every day.

Their duration was from one to four hours. Nothing that might induce an attack was noted. Their occurrence was irregular, generally early in the morning on waking, or after meals. The attacks were ushered in by nausea and nervousness. A sense of epigastric constriction soon followed and vomiting was severe during the whole attack. Palpitation was severe as the attack subsided and the vomiting ceased. Sweating was extreme at the end of an attack. During the attack there was marked vasoconstriction and coldness of the extremities; after the attack the extremities were cold and cyanotic. During attacks the blood pressure rose to the neighborhood of 260/180. The resting blood pressure varied between 150/100 and much higher, rising at times to 280/180 without symptoms. Physical examination showed the face to be habitually flushed; tremors were present suggesting Basedow's disease, and the pupils were always widely dilated. No tumor was palpated in the abdomen. Pyelograms were not done. The pulse was extraordinarily labile; it averaged around 100 and rose to 130 on the slightest provocation. The urine showed albumin to be present at times and on other occasions absent, not necessarily dependent upon whether an attack had just occurred or not. Urine was suppressed during the whole attack and appeared only several hours afterward. The patient died in an attack of pulmonary edema. The tumor in this case was in the left adrenal gland, the size of a tangerine.

Case 2 (C. H. Mayo (7), 1927). A woman of 30 years, single, a music teacher, who had been having symptoms for a year and a half. The attacks occurred about every two or three days and lasted from one-half hour to four hours. They seemed to be provoked by exertion. They occurred most frequently after breakfast. She had not been in good health, having felt run down for about 10 years. The physical examination showed some undernutrition and pallor. No tumor was palpated. Pyelograms were not done. The haemoglobin was 52 per cent; red blood cells 3.6 million. The resting blood pressure was 130/82. Special studies, including X-rays, did not reveal any noteworthy abnormalities. The attacks were ushered in by heart consciousness and palpitation. They were accompanied by lower abdominal pain and sometimes pain in the lumbar region. Sense of precordial constriction was present. Occipital headaches were severe and vomiting occurred. A cold sweat accompanied the attacks and there was a purplish mottling of the face extending to the chest. The extremities were cold, numb and tingling. The neck veins became unusually distended. Occasionally pulmonary edema accompanied the attack. The blood pressure during attacks was elevated, often exceeding 300/180, and fell rapidly as the attack wore off. The pulse was moderately accelerated during attacks. The heart was thought to be moderately enlarged during attacks; the capillaries of the nailbeds became obliterated. The patient was prostrated for several hours after such an episode. Operation was carried out and the tumor was removed. Eight years following the operation the patient seemed to be in good general health, with the symptoms entirely relived. The tumor was found mesial to the left kidney and behind the tail of the pancreas; it measured 6 x 4 centimeters.

Case 3 (Vaquez, Donzelot and Geraudel (23), 1929). A man of 37 had had

attacks for one year. They occurred at first once every three weeks but later almost daily, and sometimes several times a day. Each attack lasted several minutes. They occurred usually at the end of effort, or with emotion; sometimes without cause. There was general lassitude even between attacks. Physical examination showed some hemorrhages in the fundi. Resting blood pressure, when first seen, was 140/80; later there was permanent hypertension, 210/130. The resting pulse was 70. The urine was normal except after attacks, when it showed albumin. The attacks were ushered in by prickly sensations in the extremities, followed by cramps. The cramps then shifted from the legs to the abdomen and this was followed by precordial pain and oppression, and later by terrific headaches. Sometimes each of these symptoms occurred alone without the others. In the later attacks vomiting was present. Palpitation was marked. During attacks there was pallor, extreme coldness of the extremities. Pulmonary edema occurred in the severe attacks. The systolic blood pressure would rise to 300 and the diastolic to 180; the pulse rose from 70 to 100. X-ray was given to the adrenals and this seemed to relieve the attacks for some months, but they then recurred and the patient died in an attack. Just before death the blood urea had risen to 150 mgs. per cent. The tumor was found in the right adrenal gland; it measured 7 x 6 x 5 cms.

Case 4 (Labbe, Azerade and Violle (24), 1929). A man aged 29 had had attacks for 10–11 years and when first seen they occurred daily or several times daily; each attack lasted about one hour. A hemiplegia occurred in an attack one year before death. Aside from the signs of his hemiplegia and a systolic murmur at the base, no noteworthy abnormalities were made out on physical examination. The resting blood pressure was 160/100 and there was persistent tachycardia. Nitrogen retention varied from 80 to 150 milligrams per cent. There was albumin, 1–2 grams per liter, persistently in the urine. Attacks were ushered in by a sudden sensation of anguish. Palpitation was very marked and sweating occurred at the end of an attack. The face and extremities became markedly pale. Pupils dilated and the heart action very tumultuous. Systolic blood pressure rose to 250 or 300. The pulse rose during the attacks. The patient died in an attack of pulmonary edema. In this case the tumor was located in the right adrenal gland; it was the size of an orange.

Case 5 (Shipley (11), 1929 and Pincoffs (10) 1929). A woman of 26 who had been married for one year without pregnancies. Ten years before her first observation she had had mild attacks for four months, while playing basket-ball. Six years before observation these had reappeared; they first occurred at weekly intervals, later daily. Each attack lasted one-half to one hour. They were more apt to occur if she was nervous or worried and were very likely to come on at the same time each day. Her general health had not apparently suffered. No tumor was palpated in the abdomen, and plain plates of the abdomen were normal. Resting blood pressure was 120/90. Attacks were ushered in by hot feelings in both arms, tightness over the chest and palpitation. Severe occipital headache was present. Nausea occurred and the patient would induce vomiting with

slight relief. The whole body would shake with the severity of the palpitation. The skin showed mottled flushing and the hands were cold to the touch. Neck veins became distended. The blood pressure might rise to 260/120. The pulse usually remained below 90. Apprehension was conspicuous and there was marked tremor of the hands. Fasting blood sugar was normal and rose in the only attack so observed to 160 milligrams per cent. The patient was operated upon and seven years later was entirely free of attacks. The tumor was just above the right kidney; it weighed 150 grams.

Case 6 (Porter and Porter (25) 1930). A man of 39 had had symptoms for six months when first seen. The attacks had become more frequent than at onset, and no longer occurred only while in bed as they had at first. Each attack lasted only three to four minutes. His general health was quite good and routine examination showed no abnormalities. The resting blood pressure was 110. Urine examination was negative. There was a moderate leucocytosis and persistent slight eosinophilia, about 3.5 per cent. The assumption of a position of slight inclination forward and to the left would induce an attack in a few minutes. Attacks were ushered in by uneasy sensations in epigastrium. His color would become ashen and violent palpitation would occur. Blood pressure would rise rapidly to 200 or more and the pulse would be slowed coincidently to 55 beats per minute. The abdomen was explored and during the operation the blood pressure rose, falling when the tumor was removed. There was a good deal of "shock" for twenty-four hours after operation, but thereafter the patient's course was uneventful and he left the hospital apparently cured. The tumor here was in the right adrenal gland, the size of a kidney.

Case 7 (Rogers (26) 1932). A man of 49 had had symptoms for nine years. The attacks occurred several times daily and each lasted from ten to twenty minutes. Sometimes turning or bending, or lying on the left side seemed to induce an attack. For two years prior to observation he had had some cough and occasional hemoptysis, and symptoms and signs of diabetes mellitus had been present. There had been weight loss of twenty pounds. His complexion was florid and he looked older than his age. The heart was enlarged. The peripheral vessels were markedly sclerotic and there were old hemorrhages in the fundi. Resting blood pressure was 160/120. The liver was palpable and there was also a mass palpable in the left upper quadrant which was interpreted as spleen both on physical and X-ray examination. A moderate secondary anemia was present and the urine showed sugar and albumin. The diabetes could be controlled with insulin. Attacks were ushered in by weakness, dizziness and numbness of the extremities. Marked pallor, forcible heart beat, nausea and vomiting would occur. Blood pressure rose to 280/180. Profound sweating occurred at the end of attacks. X-ray to the adrenals was tried without benefit. The patient died as the result of chronic and acute heart failure. The tumor lay retroperitoneally in the left upper quadrant, pushing the kidney down and attached by a pedicle in the midline. It was the size of a grapefruit.

Case 8 (Suermondt (27), 1934). A 29 year old man had had symptoms for a

year and a half. At first they occurred once daily, later several times a day. Each episode lasted from fifteen minutes to two hours or more. Nothing was ever noted to induce attacks. His general health was good and the general physical examination revealed only a palpable right kidney. By pyelographic study a tumor was revealed pushing the kidney downward. The blood pressure resting was 150/115; eosinophilia, 4 per cent, was present. A trace of albumin was in the urine. Attacks were ushered in with a sensation of precordial constriction and pain. Marked palpitation was present and although the extremities felt hot to the patient, they were pale and objectively cold. Sweating was marked at the end of attacks. The blood pressure would rise to 325/200 and the pulse rate rose during attacks. After attacks albumin increased in the urine and casts appeared. Operation was carried out and the tumor was removed. Shock was present for five hours after operation but thereafter the course was normal. Operation eliminated the attacks and the blood pressure at discharge was 125/95. The tumor, the size of a fist, was in the right adrenal gland.

Case 9 (Leriche (28), 1934). A man of 41 had begun to have attacks one and a half years before, which were mild at first but had increased in intensity and frequency so that they occurred almost daily. The attacks apparently came on spontaneously and lasted one and one-half to three hours. They usually occurred while making his morning toilet. The general health had been good except that there had been intractable insomnia for four months. The general examination was normal save for hypertension (200/100) and an accentuated second aortic sound. The blood urea was 52 mgms. per cent and the urine contained some albumin and casts. After attacks the albumin was increased and glycosuria occurred. Attacks were ushered in with a beating sensation in the eyes like a pulse. Soon general arterial throbbing occurred. The extremities were markedly blanched and the neck veins greatly swollen. Vomiting occurred. Blood pressure would rise to 340/110 and the pulse usually slowed, although the slightest effort during attacks would bring on tachycardia. Blood sugar rose during attacks and closely paralleled the blood pressure. There was also evidence during attacks of concentration of the formed elements of the blood. The first exploration was carried out on the right and nothing was found. At the second operation the tumor was found, the size of a cherry, lying between the vertebral column and the aorta, independent of the adrenal. There was no postoperative shock. The blood pressure soon stabilized at 140/100. Attacks had not recurred. Albumin and casts in urine persisted. The tumor in this case was the size of a cherry and lay between the vertebral column and the aorta.

Case 10 (Kalk (29), 1934). A woman of 36 had had symptoms for nine years. They began five weeks after the birth of her first child, occurred at monthly intervals at first, but increased in intensity and severity after pregnancy until they occurred at least once daily. Each attack lasted from three to six hours. Body movements, especially bending, seemed to bring on attacks, and they seemed worse and more frequent just before the menses. Palpation of the tumor induced an attack during physical examination. The spontaneous attacks occurred

nearly always between 3 and 8 o'clock in the morning. The general health was not affected. Physical examination showed flushed facies, exophthalmic stare, widely dilated pupils, accentuated aortic second sound. There was palpable in the right upper quadrant a tender mass; this mass was apparent in the flat X-ray plate, pyelogram, and could be seen displacing the duodenum. The resting blood pressure was 120/80, the pulse 100. Attacks were ushered in with roaring in the head and deafness. Precordial pain was present which radiated to the tongue, abdomen, fingers and toes. Palpitation was marked. Repeated vomiting occurred during attacks, as well as rapid respirations, and sometimes tetany. The attacks were characterized by marked remissions and relapses, occurring at approximately three to four minute intervals. The blood pressure would rise to 300/240 and, associated with the rise, the above mentioned symptoms would occur together with marked generalized peripheral blanching. Then in three to four minutes the blood pressure would gradually fall to 90/60, and during this phase of low blood pressure the skin would be very flushed and great sweating would occur. There was no sugar or albumin in the urine at any time. Operation was carried out and the tumor was removed without untoward incidents. Two months after operation the attacks had not recurred; the blood pressure varied from 115/85 to 120/75. There was still a tendency for the patient to break out into sweats. The tumor the size of a fist, was found in the right adrenal gland.

Case 11 (Coller, Field and Durant (30), 1934). The patient was a 16 year old boy who had had symptoms for five months, episodes at first occurring two or three times a week, but later once daily. Each attack lasted several hours and no inciting factor was ever noted. The attacks generally occurred at night. The general health was good; there had been asthmatic attacks in May each year for the preceding six years. The general physical examination showed arterial changes with fresh hemorrhages in the fundi, oral sepsis, a loud systolic murmur all over the precordium, resting blood pressure 125/195. No masses were palpable in the abdomen and pyelographic studies revealed no abnormalities. The pulse was elevated. Urine contained albumin intermittently and casts in varying quantities. During attacks the patient noted precordial oppression, headache, dyspnea, profuse sweating and, occasionally, vomiting. The lips became cyanotic, the extremities cold and clammy. Pulmonary edema occurred in one attack. Blood pressure would rise to 300/200 and during an attack it would fluctuate between this level and 150/115 at approximately five-minutes intervals. Blood chemical constituents were said not to have been elevated during attacks. During operation the blood pressure rose to 300. Soon after the tumor was removed the blood pressure fell and there was marked shock; but intravenous medication and transfusion brought about a good response. Six months after operation the blood pressure was 120/80; there had been no further attacks and the retinal vessels showed improvement. The position of the tumor was lateral and superior to the hepatic flexure of the colon. It was 8 cm. in diameter.

Case 12 (Belt and Powell (31), 1934). A female of 45 had probably had attacks for about seven years before coming under observation. They had become more

severe in the two previous years. Each attack might last as long as six or seven hours. They usually occurred on first rising in the morning. The general physical examination was normal except for visible pulsations in the large vessels of the neck, a systolic murmur in the aortic area, slightly elevated systolic blood pressure (170/80), and a palpable mass in the right upper abdominal quadrant. By pyelogram the right kidney was shown to be displaced downward, rotated, and the pelvis dilated. Albumin was present in the urine and glucose appeared intermittently. During attacks palpitation and sweating were marked, vomiting occurred, and following attacks there was severe headache. In attacks the skin at first became very pale, later to be followed by flushing; and as the attacks were wearing off the skin became clammy. The blood pressure rose in attacks to 300/240. In the terminal attack the temperature rose to 107° and the patient died with pulmonary edema. At postmortem, in addition to the tumor, other abnormalities included hypertrophied heart, compression of the right kidney with dilatation of the right ureter, and congestion of the thyroid with almost complete destruction of its tissue. The tumor was in the right adrenal gland, measuring 14½ x 8 x 8½ centimeters.

Case 13 (Baker and Rienhoff (12)). A female of 40, whose symptoms had begun 11 years previously, and who had had an interval of six years when entirely free of symptoms. They had recurred toward the end of her last pregnancy, four years before coming under Dr. Baker's observation. The attacks occurred several times daily, at first were more frequent at night, lasted only a few minutes, and were induced by eating or pressure on the tumor. The terminal episode occurred immediately after the patient had taken a litre of water for a renal function study. Physical examination showed arterial changes in the optic fundi with hemorrhages, both old and new. The heart was enlarged and gallop rhythm was present. The second aortic sound was markedly accentuated, the second pulmonic moderately so. There was a palpable mass the size of a grapefruit in the left upper abdominal quadrant. Attacks were ushered in by weakness, nervousness, palpitation and dyspnea. There would be pressure sensations in the abdomen, radiating to the precordium and neck. There was severe throbbing headache. Vomiting sometimes occurred. Palpitation was extreme and great sweating accompanied the attacks. The blood pressure rose to 290/185 and the skin became very pale. There would be tachycardia and the heart sounds became unbelievably loud. The urine examined immediately after one attack was entirely negative. The patient died in an attack of pulmonary edema. Autopsy disclosed, in addition to the tumor, an hypertrophied heart. The kidneys were grossly normal, but showed, microscopically, moderate arteriosclerosis. The weight of the tumor was 560 grams and it measured 13 x 12 x 8½ cms. It lay in the left adrenal gland.

Case 14 (Pincoffs (32)). A 45 year old man had been suffering with attacks for seven months. They occurred with a frequency of two to three daily, lasted anywhere from one to ten hours. No precipitating factors were ever noted, except that attacks seemed more likely to occur about one half hour after meals.

The general health had been good except for intermittent renal colic for six months. General physical examination showed moderate undernutrition, hypertrichosis, moderate arteriosclerotic changes in the optic fundi. No abnormalities were noted elsewhere. Resting blood pressure was 140/90 but later was found to be persistently elevated. Blood, urine, and chemical examinations were normal. Attacks were ushered in with palpitation and sensations of heat around the face and trunk, and cramplike pains in the back of the neck. During attacks vertical headache was severe, nausea was present, and moderate dyspnea. Sweating was profuse. The blood pressure rose to 260/150; the extremities were very pale, with subjective and objective coldness; the ears were rosy. After attacks the urine showed traces of sugar, albumin and some casts. The blood sugar in one attack rose to 192 mgs. per cent, to 250 mgs. per cent in another. Operation was performed. There was a marked fall in blood pressure, with shock, as soon as the tumor was removed. The patient has remained free of attacks since operation. At operation the tumor was found to the right of the aorta, between the aorta and the inferior vena cava. It was the size of an English walnut, weighed 28½ grams and measured 4½ x 4 x 3½ cms.

Case 15 (Kelly and others (33), 1936). A woman of 37 had had symptoms for seven years. At first her attacks had occurred twice a month, later more frequently. The attacks seemed to be provoked by exertion, rich meals or excitement, and were worse during menses. Each attack lasted from 5 to 15 minutes. During a pregnancy the patient had been entirely free from attacks. The general health was quite good. Physical examination showed signs of extensive healed tuberculosis of the left upper lobe, enlarged cervical lymph nodes, and a palpable right kidney with some tenderness above it. Resting systolic blood pressure varied from 130 to 100; diastolic from 90 to 60. The first symptom noted in attacks was palpitation. This was followed by a sensation of fulness in the head, vomiting and sweating. The face and extremities became very pallid. Blood pressure would rise to systolic levels of 155 to 220, diastolic to between 110 and 130. In some attacks the pulse rose; in one attack it was observed to be slowed to 60. Operation was performed, the tumor was removed, and the postoperative course was uneventful. The attacks had not recurred at the time of publication. At operation the tumor was found in the right adrenal, 10.5 cm. in diameter and weighing 240 grams.

Case 16 (Volhard (34), 1931). A physician 38 years old had had symptoms for seventeen months. At first, attacks occurred only occasionally, later three to four times daily. Each attack lasted about five minutes. They seemed to be induced by bending over backwards and by the performance of such acts as shaving and gargling. Physical examination showed a marked degree of hemorrhagic retinitis with exudates; also a slightly enlarged heart. The resting systolic blood pressure was at first 145; within a year it had risen to 180/130. No abnormalities were palpable in the abdomen, and pyelograms were negative. The urine when first seen was normal, later showed albumin. Attacks were characterized by dizziness, weakness, occipital headache, palpitation. During attacks there were

eivdences of peripheral vasoconstriction, usually universal, but many times only the upper half of the body was involved, sometimes only the neck; frequently sweating seemed more profuse over the left side of the body than the right. The pallor was soon followed by redness of the skin. During the attacks the blood pressure rose as high as 330/120. The pulse was slowed at first, later increased. Albumin in the urine was found increased after attacks. Exploratory operation was performed. To the operator the right adrenal appeared normal; the left seemed enlarged and was removed. The next day the patient gave a sudden cry and died. At autopsy an egg-sized tumor was found in the right adrenal. The brain was not studied and the cause of sudden death remains unexplained.

Case 18 (Burgess, Waterman and Cutts (35), 1936). A 25 year old woman had begun to have attacks two years prior to coming under observation, four years prior to her death. As the duration of the disease progressed the attacks occurred once daily; they had been less frequent at onset. They usually occurred at night; their duration varied from a few minutes to several hours. The general physical examination showed downward displacement of the right kidney and compression of its upper pole. The resting blood pressure was 120/80. The urine was normal save for slight glycosuria on several occasions; the relationship of the glycosuria to the attacks was not noted. Attacks were characterized by severe headache, palpitation, vomiting and on certain occasions by pulmonary edema. During attacks the skin was pale and the neck veins were distended. Later in the disease the blood pressure showed remarkable fluctuations during attacks, rising to 240/180 and falling to 65/40 at intervals of approximately fifteen minutes. During periods of rising pressure the pulse was slowed; while the pressure was falling or low the pulse was accelerated. Operation was performed. There was a fall in blood pressure soon after the anesthetic was begun, and during operation the blood pressure was unobtainable. The tumor was removed but shock persisted. Intravenous glucose seemed to bring about improvement but at the completion of the injection pulmonary edema occurred and the patient died. Operation revealed the tumor in the right adrenal gland. It was 9 cm. in diameter.

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PRIMARY CARCINOMA OF THE TRACHEA WITH CUTANEOUS CARCINOMATOSIS

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Primary carcinoma of the trachea occurs very infrequently. Extensive reviews of the literature of the subject were made by Lombard and Baldenweck (10) in 1914, by Broman (1) in 1924, by D'Aunoy and Zoeller (3) in 1929, and more recently by Culp (2). According to Culp 147 cases have been reported.

The tumor is usually an adenocarcinoma or a squamous cell carcinoma, arising from the posterior wall of the trachea near its bifurcation. Males are more commonly affected than females. The incidence is greatest in the fifth and sixth decades. Metastases are usually regional but generalized dissemination does occur. The esophagus and lungs may be involved by direct extension of the tumor growth.

The symptom-complex is that of an obstructive lesion in the tracheobronchial tree. Cough and breathlessness on exertion are often the first symptoms. Later, respiration may become wheezing so that the patient will complain of "asthma." The sputum may, or may not, be bloody. Hoarseness, dysphagia and loss of weight appear still later and depend in large measure upon the location and the extent of the lesion.

It is rare for carcinoma of any organ to metastasize to the skin, but it does so occasionally. Carcinoma *en cuirasse* following primary malignant disease of the breast is not an exceptional eventuality. Kaufmann-Wolf (9) collected a series of 65 patients in whom metastases to the skin developed from carcinomata of the internal organs. The majority of these were instances of carcinoma of the stomach. Two were primary in the bronchi, and three originated in the parenchyma of the lungs, but there was no instance of tracheal neoplasm. Junghanns (8) studied 405 cases of carcinoma of the respiratory tract. Three hundred and ten (310) were carcinoma of the lung or of the

bronchi and only 4 originated in the trachea. Metastases to the skin occurred in about one per cent of those cases involving the lung or bronchi. No mention was made of metastases from tracheal carcinoma.

Carcinoma of the lung or bronchi occurs frequently but it is uncommon for either of them to metastasize to the skin. Fried (6) in his exhaustive monograph on carcinoma of the lung does not mention such a case. Out of 15,380 autopsies performed at this hospital there are 28 cases of carcinoma of the bronchus and 46 cases of carcinoma of the lung. Metastases to the skin were not found at any of these autopsies. On the other hand, although comparatively few cases of tracheal carcinoma have been reported, metastases to the skin have been met with. Fraenkel (5) and Broman (1) each reported cases with cutaneous involvement. Figi (4) reported a case with a mass in the left frontal region which suggested, but never was proved to be, a skin metastasis.

Skin metastases would then seem to occur more commonly in carcinoma of the trachea than in carcinoma of the lung or bronchi. The clinical value of such an observation, though inviting, is probationary. Nevertheless, it is interesting that the first and only case of carcinoma of the trachea out of 15,380 autopsies at this hospital should have had widespread dissemination of the tumor nodules throughout the skin.

Because carcinoma of the trachea is rarely observed; and, because skin metastases, though uncommon, seem to occur more frequently in carcinoma of the trachea than in carcinoma of the lung or of the bronchi, the following case is reported.

The patient, G. E. C., Med. 100711, a seventy three year old widower and retired railroad clerk was admitted to The Johns Hopkins Hospital, on the service of C. R. A., February 28, 1937, because of pain in the right chest, cough and loss of weight of six weeks' duration.

The family history was irrelevant.

The patient had always enjoyed good health until December, 1933, when he was admitted to the Brady Urological Clinic, of The Johns Hopkins Hospital, because of symptoms that were proved due to benign prostatic hypertrophy. During his stay in the hospital he developed bronchopneumonia from which he recovered promptly and completely, and he was finally discharged without undergoing treatment for the prostatic condition.

He remained fairly well until the fall of 1936 when he developed a constant, aching pain in the lumbo-sacral region which his attending physician felt was related to the chronic prostatic hypertrophy. He improved after a vacation but about six weeks before his admission to this hospital he became hoarse and the hoarseness was so severe at times that he was aphonic. Shortly thereafter a cough productive of odorless and bloodless muco-purulent sputum developed. Concomitantly he became aware of a dull, aching pain in the upper right chest that was accentuated by deep inspiration. The symptoms increased gradually in intensity and before long, night sweats and bloody sputum developed. During the illness which preceded his admission to the hospital he lost about 15 pounds in weight.

Physical Examination: Temperature 99.6 (Mouth). Pulse 100. Respirations 20.

The patient was a sparely nourished, elderly man, propped up in bed without evident discomfort. There was apparent loss of weight. There was no cyanosis or clubbing of the fingers. The voice was not husky. The pupils were equal, regular and reacted normally. Arcus senilis was marked. There was no struma or disturbance of the extra-ocular movements. The trachea seemed to be in the mid-line. There was no localized or generalized lymphadenopathy. Two small subcutaneous nodules were found beneath the right clavicle. The nodules were firm, freely movable, attached to the skin and the skin overlying them was not discolored. Two other similar nodules were found high in the left anterior axillary line and one posteriorly over the right scapula. The thorax was narrow and deep. There was a marked gradual bowing of the thoracic spine, no actual gibbus, but the spine over this area seemed rigid and tender. No sensitiveness could be elicited over other bones of the skeleton. The percussion note was resonant throughout the left lung, but was distinctly impaired in the right interscapular region and to the right of the manubrium in the second and third interspaces. The lung bases were in relatively normal position and freely movable. The breath sounds were a little more distant in the right interscapular region than in the corresponding area on the left side though not modified appreciably and not accompanied by râles. Elsewhere throughout the chest the only abnormality noted was a slight prolongation of expiration. The examination of the heart was negative with the exception of a loud musical systolic murmur at the apex. The second pulmonic sound was normal. There was no palpable pulsation in the episternal notch. The pulse was regular and of good volume. Blood pressure, 144/64. The vessel walls were diffusely thickened. With the exception of a moderately enlarged and boggy prostate the remainder of the physical examination was essentially negative.

Laboratory Data: The blood Wassermann reaction was negative. The blood non-protein nitrogen and sugar, on admission, were 44 and 94 mgms. per cent, respectively. The red blood cell count was 5,500,000 on admission and fell to 3,500,000 before death. The hemoglobin was 14.7 gms. (102%) and dropped proportionately with the red count before exitus. The white blood cell count remained between 10,000 and 12,000. The differential white cell count was always

normal. The sputum was muco-purulent and contained old blood. It did not contain tubercle bacilli, fungi, or spirochetes, but showed constantly numerous gram-positive cocci and gram-negative bacilli. The stool and urine examinations were always negative. X-rays of the chest revealed an area of dense infiltration at the root of the right lung which radiated into its upper and middle lobes. The ninth rib was partially destroyed.

Clinical Impression: Carcinoma of the right main bronchus extending into the upper and middle lobes of the right lung, with metastases to the thoracic spine, right ninth rib, and to the subcutaneous tissues. Generalized arteriosclerosis. Benign prostatic hypertrophy.

Three days after admission a biopsy of the nodule over the right scapula showed carcinoma, an exact classification of which could not be made. The original

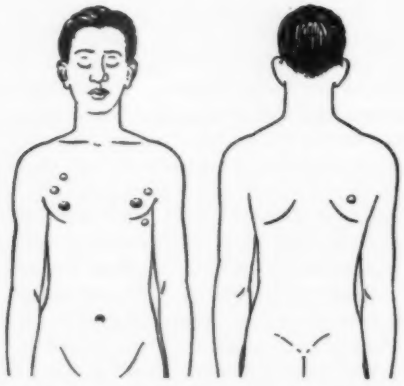

FIG. 1. Drawing to illustrate the distribution of the subcutaneous nodules on the day of admission to the hospital.

nodules became larger and new ones appeared, literally, over night. Figure 1 and Figure 2 illustrate the dissemination that occurred during the nine days following admission to the hospital. By March 24 (Figure 3) the skin anteriorly and posteriorly over the thorax was peppered with these lentil-like nodules and a few had appeared in the skin of the abdomen. By April 8 (Figure 4) just 6 days before death, they had become too numerous to count. The nodules varied in size from 2 mm. to 2 cm. in diameter. None was ulcerated. One nodule was noted in the skin over the posterior portion of the right arm, but none developed elsewhere in the extremities.

The course was progressively down hill and exitus from bronchopneumonia occurred on April 14, 45 days after admission.

Post-Mortem Examination. (Autopsy No. 15272. Performed by Dr. Louis Hamburger, Jr.)

The body was that of an emaciated seventy three year old man. The distribution of subcutaneous nodules is illustrated in Figure 4. The eyes, ears and

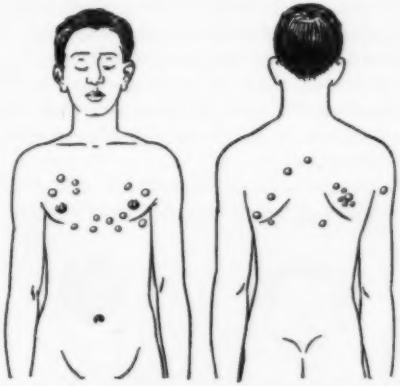

FIG. 2. Drawing to illustrate the dissemination of the subcutaneous nodules that accrued during the 9 days following admission to the hospital.

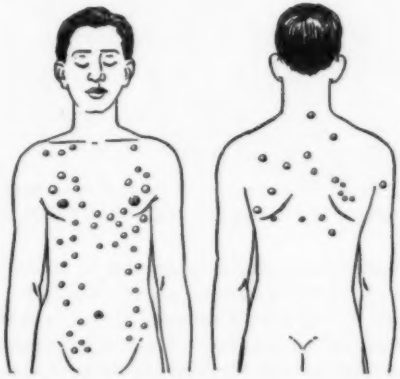

FIG. 3. Drawing to illustrate the dissemination of the subcutaneous nodules that accrued during the 25 days following admission to the hospital.

nose were normal. There was anodentia. The genitalia and extremities were normal.

There was no free fluid in either pleural space. The right lung was densely adherent to the lateral chest wall. The left lung was collapsed. The pericardium was delicate and the pericardial cavity contained a normal amount of clear fluid.

The heart was small. The coronary arteries were tortuous and sclerotic. The epicardium was opaque in many places. The tricuspid valve was normal. There was extreme calcification of the cusps of the aortic valve. There was a tetracuspid pulmonic valve. The base of the mitral valve adjacent to the aorta was thickened with deposits of lipoid material. The left ventricle was thinned out toward the apex and showed a large area of scarring. On the surface of the left ventricle, near the apex, there was a small cluster of superficial, elevated, pearly nodules which, on section, were white and suggested tumor metastases.

The aorta was stiffened by many calcified plaques which were especially prominent near the bifurcation.

The lungs were emphysematous and beneath the pleural surfaces of both there were many firm, white nodules. About 2.5 cm. above the bifurcation of the

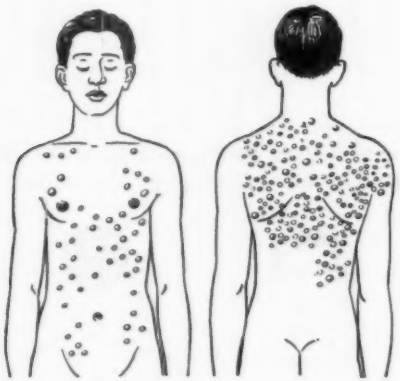

FIG. 4. Drawing to illustrate the distribution of the subcutaneous nodules 39 days following admission to the hospital and 6 days before death.

trachea there was a gray nodule that extended into its lumen from the right side This nodule was about 1.5 cm. in diameter and projected 4 mm. into the trachea. Tissue similar to that of this growth extended through the wall of the trachea into the adjacent tissue and there formed a dense gray mass about 4.5 cm. long by 2.5 cm. wide that occupied a position between the trachea and the apex of the right lung. In it were embedded some anthracotic lymph nodes which were almost completely replaced by tumor. Although there was continuity between the nodule that projected into the trachea and the tumor tissue without it, the tracheal cartilages had not been destroyed and the rings could be seen plainly. None of the bronchi contained or were invaded by tumor masses. There was a fragment of a large artery embedded in the tumor mass outside of the trachea and its wall appeared to be invaded by the tumor. Many small tumor nodules were scattered

throughout the parenchyma of both lungs. In the apex of the left lung there was a flat scar that was covered by thickened pleura. There were patches of confluent bronchopneumonia in the lower lobes of both lungs.

There was no free fluid in the peritoneal cavity, and the peritoneal surfaces were smooth and glistening and the organs were in their normal positions. Scattered in the mesentery were many, small, white nodules which appeared grossly to be tumor tissue. There were similar nodules, ranging in size from a few millimeters to 3 cm. in diameter, scattered throughout the liver, the gall-bladder, the spleen, the pancreas, both of the adrenals, the left kidney, and the vertebrae. The mesenteric, retroperitoneal and pelvic lymph nodes also contained tumor

FIG. 5. Photograph of the left lower thorax, the left upper abdomen and the left arm taken one day before exitus, which illustrates the subcutaneous nodules.

tissue. About 1 cm. above the pylorus there was an oval, cleanly punched-out ulcer with a smooth base. This ulcer measured 6 mm. in its greatest diameter. The ureters, the urinary bladder, the seminal vesicles and the testes were normal, but there were nodules in both lateral lobes of the prostate.

The esophagus and neck organs were normal.

The femur bone marrow was fatty.

The brain was not obtained for examination.

The following is Dr. William G. MacCallum's histological description of the tumor tissue. "It seems that the most probable origin of the tumor is in the trachea above the bifurcation. There, the mucosa is largely replaced by the tumor although some of the mucus-secreting glands persist and are embedded in

the tumor tissue. The growth extends between the cartilages of the trachea and outside forms a large mass most of which is completely necrotic, although the forms of tumor cells and blood vessels can still be seen faintly. The tumor has not retained the form of the cylindrical lining cells of the trachea nor has it even developed a distinct gland-like structure. Instead, the cells are variable in form and in general are arranged in solid masses. Some of these masses are a little elongated while others are rounded. The tumor cells are distinctly epithelial cells and whatever the size or shape of the strand of tumor, the stroma is well marked off and preserved. In a few places there is a suggestion of an adenocarcinomatous arrangement. The tumor metastasizes into the skin, the epicardium, the lungs, the thyroid, the bones, the adrenals, the left kidney, the liver, the pancreas, the spleen, the gall-bladder, the perirenal tissue, the mesentery, the prostate and the peribronchial, peritracheal, mesenteric, retroperitoneal and pelvic lymph nodes. Everywhere the type of the tumor is the same. In the small intestine there is a tumor nodule over which the mucosa has disappeared so that it appears as a shallow ulcer."

Anatomical Diagnosis: Carcinoma of the trachea with metastases to the lungs, the skin, the epicardium, the liver, the gallbladder, the spleen, the pancreas, the adrenals, the left kidney, the thyroid, the prostate, the perirenal tissue, the mesentery, the vertebrae, the ninth rib, the ileum, and the peribronchial, peritracheal, mesenteric, retroperitoneal and pelvic lymph nodes. Generalized arteriosclerosis. Extreme calcification of the cusps of the aortic valve. Tetracuspid pulmonary valve. Ulcer of the pylorus. Bronchopneumonia. Emaciation.

DISCUSSION

Although it is not the purpose of this article to discuss in detail the theories that have been advanced to explain the parietal dissemination of carcinomatous implants, a plausible explanation for this rare clinical development is presented. Because parietal dissemination is the result of actual cancerous growth along the lymphatics of the skin, the anatomy of these vessels is reviewed briefly:

The lymphatics of the skin originate in the papillae as small, blind end-sacs and the vessels that arise from them join to form small cutaneous networks. Each network empties into a separate tributary which runs vertically through the subcutaneous tissues to join the fascial lymphatic plexus which is their only means of inter-communication. From the muscles there are similar tributary communications that run upward to join the fascial plexus. This great plexus is divided by the median plane of the body, and also by two horizontal planes that pass through the clavicles and the umbilicus,

respectively, whereby three anastomosing systems of lymphatic drainage are formed for the skin of each side of the body. The superior system is drained by the cervical, the medial system by the axillary and the inferior system by the inguinal lymph nodes.

In his studies on cutaneous carcinomatosis in malignant disease of the breast, Handley (7) has shown that there is actual cancerous growth along the fascial lymphatics and that this growth is independent of the direction of lymph flow, proceeding with ease either with or against the lymph stream.

Carcinomatous implants in the skin make their appearance in the form of isolated nodules between which there is no connection. Handley has demonstrated that these nodules are formed by an actual extension upward of the permeating growth through the vertical lymphatic tributaries from the fascial plexus.

The anastomotic fascial systems, described above, which divide the body into six areas of lymphatic drainage form efficient barriers against retrograde embolic dissemination of a neoplasm, but they are unable to thwart the advance of a permeating growth. Thus it is easy to understand, that the development or cutaneous carcinomatosis may occur whenever the fascial lymphatic plexus is invaded by a neoplasm, and it is reasonable to believe that the parietal dissemination of the tracheal carcinoma, which occurred in the patient that we have reported, developed in such a way.

The results of our study suggest that if cutaneous metastases occur in a case of tracheo-bronchial obstruction, the primary growth is more likely to be located in the trachea, than in the parenchyma of the lungs or in the bronchi.

I wish to express my gratitude to Dr. Charles R. Austrian, for his generous suggestions, to Dr. William G. MacCallum and Dr. Louis Hamburger, Jr., for the use of the pathological data, and to Mr. Shriram Deshaprabhu, for the figures which he so kindly sketched.

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CONGENITAL CARDIAC MALFORMATION PRESENTING COMPLETE INTERRUPTION OF THE ISTHMUS AORTAE WITH TRANSPOSITION OF THE GREAT ARTERIES

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This report of a congenital cardiac malformation is prompted by the unusual nature of the anatomical deformity as indicated by its absence from the Johns Hopkins Hospital records of 15,000 autopsies and by failure to discover an exactly similar example in the abundant literature pertaining to the general subject of congenital heart disease.

CASE REPORT

J. A. F. (2/2/1937), a white male infant, three weeks old, was brought to the Harriet Lane Home (H. L. H. No. A-778) with the complaint of "heart trouble."

The family history was non-contributory to the complaint.

The infant's illness dated from birth and was characterized by deep, persistent cyanosis and difficulty in breathing.

The physical examination revealed an extremely ill, intensely cyanotic infant, gasping for breath and coughing frequently. The respiratory rate was 48 per minute; the temperature registered 36.6°C. The pulse rate was 140 per minute. The heart was markedly enlarged, especially to the left, and the sounds were much exaggerated. A systolic murmur was heard over the entire precordium. The lungs were clear. The liver extended to the level of the umbilicus. The pulse was obtained in both arms and legs. The cyanosis, which was much more pronounced in the upper half of the body, was sharply demarcated at a line just beneath the level of the umbilicus, below which the blood supply to the skin seemed fairly well aerated.

The laboratory examination revealed the following essential findings: erythrocytes 5,000,000; haemoglobin 140%, leucocytes 19,000. The roentgenologic examination showed a greatly enlarged heart with a narrow aortic shadow and the absence of a pulmonary conus shadow. The electrocardiogram demonstrated high P waves in Leads 2 and 3 and a T wave of low amplitude in Lead I. There was no axis deviation.

The infant suffered from repeated attacks of extreme dyspnoea. He took his feedings poorly and steadily lost ground. One week after admission, at one month of age, he died.

The symptoms and signs presented by the patient during his brief life were attributed to a congenital malformation of the heart with a permanent venous arterial shunt.

Autopsy report

At autopsy no gross or microscopic abnormalities were noted except those which referred directly to the heart and large vessels. The following is Dr. W. G. MacCallum's description of the gross appearance of the heart and the relation of the great vessels:

"The heart shows a transposition of the arteries, the aorta arising from the right ventricle. The right auricle exhibits an open foramen ovale which is guarded by a valve. The fossa ovalis measures at least 12 x 8 mm. but the actual opening into the left auricle measures 8 mm. The aorta springing from the right ventricle shows the orifices of the coronary arteries. The aorta extends upward and gives rise to the innominate, the left carotid and subclavian and then stops. At the beginning of the left subclavian, there is a tiny yellow patch on the lining of this vessel with a central depression and a minute projection on the outer surface. This projection is interpreted as the remnant of the isthmus aortae. The left ventricle has a thick wall. There is a perforation of the septum membranaceum and this opens just behind the tricuspid valve and below what is analogous to the conus pulmonalis. The left auricle receives the pulmonary veins in normal fashion. The auriculo-ventricular valve (whether to be regarded as tricuspid or mitral) seems rather normal. From the left ventricle there passes out a large artery which gives off the two pulmonary branches and goes on without interruption into the descending aorta. The connecting portion between the pulmonary vessels and the descending aorta must be regarded as a widely patent ductus arteriosus. The isthmus of the aorta has disappeared completely except for the slight projection mentioned above at the root of the subclavian artery. The descending arch and descending aorta proceed normally."

DISCUSSION

The outstanding clinical features were: (*a*). Intense cyanosis of the upper extremities extending just below the level of the umbilicus and much less cyanosis of the lower extremities; (*b*) strong pulsation in both arms and legs; (*c*) roentgenological evidence of cardiac enlargement with a narrow aortic shadow and no shadow representing the pulmonary conus; (*d*) the electrocardiogram showed T waves of low amplitude in Lead I.

At autopsy there was demonstrated transposition of the large arteries with complete interruption of the aortic isthmus. The descending aorta was continuous with the pulmonary artery through a patent ductus arteriosus.

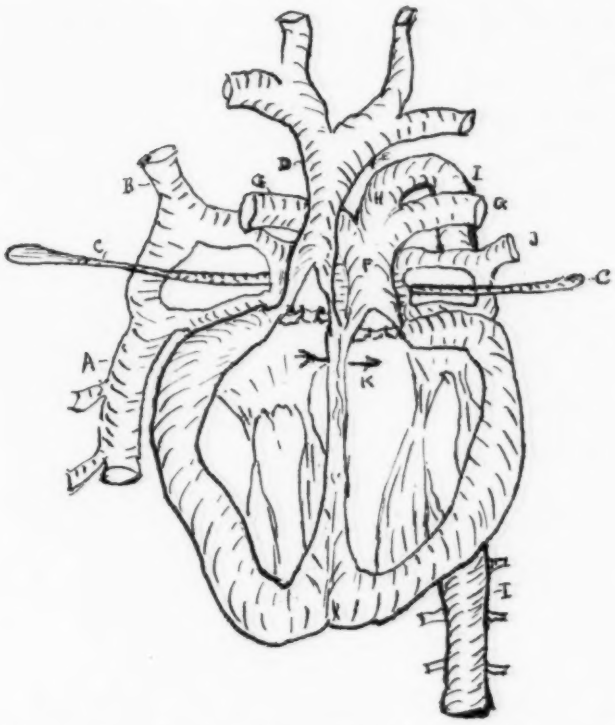

FIG. 1. DIAGRAM OF THE CIRCULATION AS SHOWN IN FIGURE 2

A, inferior vena cava. *B*, superior vena cava. *C*, probe passed through the foramen ovale. The relation of the valve is shown in figure 3. *D*, aorta springing from the right ventricle, showing the coronary orifices and giving off the innominate artery and the left carotid and subclavian. At *E* there is a minute projection which may represent the remnant of the isthmus aortae. *F*, pulmonary artery giving off the main trunks to the lungs (*GG*). *H*, the wide open persistent ductus arteriosus continued into the descending arch and dorsal aorta (*II*). *J*, pulmonary vein of which only one is shown, entering the left auricle. *K* indicates the minute orifice in the septum ventriculorum also shown in figure 3.

The circulation of the blood was evidently greatly distorted, as shown by the extreme cyanosis of the upper part of the body contrasting with the appearance of the lower half. This is explained by

the malformation illustrated in the diagrams and photographs. Both superior and inferior venae cavae, carrying all of the venous blood, entered the right auricle and thence passed the blood into the right ventricle, except for such an amount as could go through the foramen ovale, which was guarded by its valve, into the left auricle. From the right ventricle it passed into the transposed aorta, filling the cor-

FIG. 2. HEART AS SEEN FROM IN FRONT, SHOWING MUCH OF WHAT IS DRAWN IN FIGURE 1

Unfortunately the ductus arteriosus was torn somewhat by a ligature, but the absence of the isthmus aortae is plain.

onaries and going on to the head and arms and thorax, but with no access to the rest of the body (figs. 1, 2).

To the left side of the heart the only external source of blood was the amount which passed through the foramen ovale, since it drove the blood through the pulmonary arteries into the lungs, received it back again through the pulmonary veins emptying into the left auricle, and

sent the remainder through the wide ductus arteriosus into the continuation of the aorta to the lower part of the body. This was the only oxygenated blood, and while it sufficed readily for the intercostal arteries and those of the abdominal viscera and lower extremities, it returned as venous blood to the right side and as such supplied the brain and upper half of the body.

In the normal heart in which abundant blood from the right ventricle through the pulmonary circulation fills the left auricle with oxygenated blood, the pressure relations between the two auricles, the right receiving all the venous blood, cannot be very important, but sufficient at least to demand that the valve over the fossa ovalis be so arranged as to prevent the passage of blood from the left auricle into the right. The complete closure of the foramen in most adults seems to be evidence of this. But in our case, since there was no other entry for blood into the left side of the heart, and since the auriculo-ventricular valve and the valve over the foramen ovale were normally formed and quite competent (fig. 3), the left side of the heart would in two or three beats become perfectly empty; and the pressure in the left auricle reduced to zero except for the flow of venous blood from the over-filled right auricle into it through the wide open foramen ovale. This, then, was the sole source of blood for the circulation kept up by the left side of the heart.

Even if the left auriculo-ventricular valve had been defective so that the large muscular left ventricle could have affected the pressure in the left auricle, it seems that the great mass of the venous blood could hardly have allowed the entry of much oxygenated blood from the left into the right auricle. But the valve covering the fossa ovalis was normally placed so as to render impossible the passage of blood from the left to the right auricle, and the auriculo-ventricular valve was quite competent, so that the possibility of passage of oxygenated blood from the left auricle may be dismissed. There remains only the minute opening in the ventricular septum which could have allowed the entry of enough aerated blood from the left ventricle to the right to account for the maintenance of *any* aeration of the blood passing to the brain. The extremely small size of this opening (1 millimeter; see fig. 3) makes it seem difficult to account for the continuation of life in a child whose brain was receiving prac-

tically only venous blood. There is, of course, the remote possibility that there may have been some collateral arterial circulation established between the intercostal arteries springing from the aorta below the interruption at the isthmus, and the profunda cervicis or even

FIG. 3. SHOWS THE PROBE THROUGH THE FORAMEN OVALE AND THE NORMAL ARRANGEMENT OF THE VALVE ALLOWING THE PASSAGE OF BLOOD FROM RIGHT TO LEFT AURICLE ONLY

The minute orifice in the septum ventriculorum is plainly seen

branches of the carotids, or vertebrals, but this, unfortunately, was not established by injection as could perhaps have been done at autopsy.

The coronary blood supply to the heart walls was also of this non-oxygenated or venous character since it came from the aorta arising

from the right ventricle and it seems that this is in agreement with the clinical observation that low T waves in the electrocardiogram, such as were recorded in the present case, frequently occur in cases of insufficient coronary circulation.

Except, therefore, for the minute interventricular septal defect which could account for some admixture of oxygenated blood with that propelled and received by the right side, that current was wholly venous; while the left side was concerned only with circulating through the lungs such blood as it received through the foramen ovale, and then pouring it out into the lower half of the body.

The early literature on the subject under consideration is contained in Peacock's *Malformations of the Human heart* (1866) (1). Here there are references to three cases of complete disunion of the ascending and descending portions of the aorta, the first being Steidele's, published in 1812. In none was the anomaly associated with transposition.

Herxheimer (2), in 1910, stated that nine cases of entire absence of the aortic arch had been reported up to that date, but a critical study of his data shows that this figure should actually have been seven. In his review there is classified under the caption of transposition a case exhibiting a congenital absence of the isthmus aortae. The case is that of Seidel reported in 1818. Letterer (3) subsequently (1922) challenged Herxheimer's interpretation of Seidel's latin text and concluded that there was no evidence of an associated transposition in Seidel's specimen. Letterer referred to the contribution of a tenth example of complete interruption of the arch by Berblinger and adds a case of his own. In an article in *Nelson's System of Medicine* published in 1932, Maud Abbot (4) mentions another instance of this anomaly, while in 1933 Evans (5) described three further examples. Thus, until now, only thirteen cases of complete interruption of the isthmus aortae have been recorded. This malformation is, therefore, extremely rare but when, as in our case, it is associated with transposition of the great arteries, the combined malformation yields, perhaps, a unique specimen. The closest approach to it is furnished by Abbott's case. In her description of it she states that there existed not only complete absence of the aortic arch but also a "persistent ostium primum, defect of the interventricular septum . . . the aorta

arising from the right ventricle in true transposition." Furthermore, she writes that she knows of two other similar cases in "museum collections." Abbott's specimen differs from ours, since in the present case the common interauricular and interventricular septum is normally formed.

While the ultimate cause of a malformation such as we have just described is unknown, the pathogenesis of aortic isthmus atresia, according to most investigators, involves an atrophy of the fourth aortic arch and the persistence of the fifth which forms the ductus arteriosus. The discussion of the possible mechanism concerning the origin of transposition lies beyond the province of this brief report.

SUMMARY

An unusual congenital cardiac malformation is herewith presented, in which complete interruption of the aortic arch is associated with transposition of the great arteries. A review of the literature discloses thirteen cases of complete atresia of the isthmus aortae. In only one of these was there also transposition and this one was complicated by a large interventricular septal defect and persistence of the ostium primum.

I am deeply indebted to Dr. William G. MacCallum for his constant interest and invaluable help. I wish also to extend thanks to Dr. Edwards A. Park for his permission to include the clinical data, and to Dr. Helen B. Taussig for her assistance in assembling this material. The photographs were made by Milton Kougl.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Text Book of Surgical Nursing. By HENRY S. BROOKS, JR., M.D. 636 pp. Illus. $3.50. (*The C. V. Mosby Company, St. Louis, 1937.*)

The book is well organized, the subject matter being divided into chapters which follow one another in logical and well planned sequence. The information is presented concisely and is of a very practical type. Special effort has been made to coördinate the work of the surgeon with that of the nurse. The illustrations, of which there are many, both photographs and drawings, are unusually good.

Several chapters are outstanding in that they present simply and clearly much practical information. Among these I would include the chapters on "Dressing Room Technique" and "The Operating Division."

The chapter dealing with "Instruments, Sutures and Drains" might perhaps have been omitted. Very little knowledge of instruments can be obtained from pictures, and the tabulation of instrument lists for various operations seems of little value because these vary not only with each hospital but even with individual surgeons in the same hospital. A second criticism is that the paragraph headings in black type are sometimes misleading. For example, "Carbon Dioxide Routine" goes on to discuss the proper method of lifting a patient from stretcher to bed, the importance of turning postoperative patients, and the desire on the part of the surgeon to keep patients quiet after operation by administering sedatives, etc.

These are only minor criticisms. As a whole, the text is very worth while, particularly since it is expressed in language which is simple enough to be easily comprehended by the average student nurse.

A. D.

Von der Fürtrefflichkeit und Nutz der Anatomy, von WILHELM FABRY von Hilden genannt FABRICIUS HILDANUS. *H. R. Sauerländer and Co., Aarau, Leipzig.* 1936 [Veröffentlichungen der Schweizerischen Gesellschaft für Geschichte der Medizin und der Naturwissenschaften X]. XVI + 203 pp.

Fabricius Hildanus, who was born in 1560 in Hilden near Düsseldorf, died in 1634 in Bern, the greatest surgeon of his time in the German speaking countries. In 1624 he published a book on the excellence and use of anatomy of which in later years he prepared a second and enlarged edition. The manuscript of this 2nd edition, which passed over to the municipal library of Bern, has now been edited by Professor F. de Quervain and Dr. Hans Bloesch in collaboration with Dr. Th. de Quervain.

The aim of the book was to point out the necessity of anatomical studies not only for physicians and surgeons, but also for government officials. Full of illustrative examples, taken chiefly from Hildanus' own practice, it gives a good insight into medical conditions about 300 years ago when a midwife could practise for 30 years without knowing of the existence of the uterus (cf. p. 46). The book represents an interesting specimen of popular scientific writing of that time and will make delightful reading for anyone who likes the rough and clumsy yet vigorous German style of the period.

O. T.

Maternity and Post-Operative Exercises. By MARGARET MORRIS. 152 pp. Illus. $2.00. (*Oxford University Press, New York, 1936.*)

Moderate exercise in pregnancy and carefully graded movements during the puerperium are of established value in promoting the health of the parturient woman and in restoring the tone of her abdominal and perineal muscles after delivery. This small volume describes in detail some twenty-one exercises suitable for women at this time. Included are a number of exercises designed to instruct and train the prenatal patient in certain important muscular efforts which will be needed during the second stage of labor, particularly contraction of the abdominal muscles with simultaneous relaxation of the perineum. The exercises described are sound in principle and their general employment should bring about beneficial results. The book will fulfill a useful purpose if it serves only to remind obstetricians of this neglected field.

N. J. E.

Neurology. By ROY R. GRINKER. 2nd ed. revised. 999 pp. Illus. $8.50. (*Charles C. Thomas, Springfield, Ill., 1937.*)

This is much more than a textbook of clinical neurology. The author regards neurology as one of the biological sciences and deals with the science as well as with the art of neurology. There are sections devoted to the comparative anatomy of the nervous system, to physiological and anatomical embryology, to neuro-anatomy and to neurophysiology. There is, moreover, a much fuller discussion of pathological anatomy than is usual in textbooks of neurology. The latest results of experimental investigations are given in considerable detail especially as regards work on the vegetative nervous system. There is a section devoted to cortical action currents and to electroencephalography. There is, however, no mention of psychology or of the psychoses. Evidently the book will hold as much interest for those engaged in investigating the anatomy and physiology of the nervous system as for clinical neurologists.

The book is beautifully designed and printed and is abundantly illustrated with photographs of patients, diagrams of the anatomy of the nervous system, photographs of gross lesions and photomicrographs of various pathological processes.

F. R. F.

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This book seeks to give the story of the development of Mall's mind and its influence on medical science and on medical education. The writer worked for twenty years under Mall and the theory of education outlined in this volume was thus learned directly from him. It is hoped that the new generation of medical students who have never known Mall may gain, through these pages, some idea of how this man has influenced their lives and that, too, they may gain an insight into the difficulties through which the generation that preceded theirs won the privileges they now enjoy. Mall is but little known to the public, but one has only to mention his name to any of his colleagues to sense that he was one of the leaders of his generation.